SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER

A SINGLE ARM PROSPECTIVE STUDY

INSTITUTION

BARNARD INSTITUTE OF RADIOLOGY AND ONCOLOGY
DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
&
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CERTIFICATE

This is to certify that **Dr. S. VIJAYAKUMAR** has been a Post Graduate MD Student during the period from may 2012 to April 2015 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER"**is a bona fide work done by him during his study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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I solemnly declare that the dissertation titled

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A **SINGLE ARM PROSPECTIVE STUDY** was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during my study period, under the guidance and supervision of Prof. Dr. S. SHANMUGAKUMAR, B. Sc., M.D.,RT.

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CONTENTS

ABBREVIATIONS

1. SCCHN : Squamous Cell Carcinoma of Head and Neck
2. HNC : Head and Neck Cancer
3. HPV : Human Papilloma Virus
4. ECOG : Eastern Cooperative Oncology Group
5. PS : Performance Status
6. PRT : Palliative Radiotherapy
7. SAS : Symptom Assessment Scale
8. BSC : Best Supportive Care
9. MMTR : Madras Metropolitan Tumor Registry
10. RECIST : Response Evaluation Criteria In Solid Tumors

SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER

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ABSTRACT

INTRODUCTION

In our country, majority of patients with head and neck malignancies present with locally advanced disease. Most of these patients are often found unfit for radical surgical treatment or chemo radiotherapy approaches due to poor general condition and poor nutritional status. These advanced head and neck cancer patients need Palliative Anti-cancer therapy and/or best supportive care (BSC).

AIM AND OBJECTIVES

Primary Objective:

To assess for degree of symptomatic relief & palliation.

To assess the proportion of patients eligible for radical chemo radiotherapy.

To assess immediate loco-regional disease control.

Secondary Objective:

To assess the acute toxicity to the treatment.

MATERIALS AND METHODS

30 advanced and unresectable head and neck cancer patients who attended department of radiotherapy were included in this study.

All patients were treated with 20Gy radiotherapy in 5 fractions of 400cGy each. Response will be assessed after 1 month of radiotherapy. Patients achieving symptom relief of more than 50% and partial response at primary/nodal sites with good general condition were treated with further chemo radiotherapy at curative intent in 200cGy/# upto a total radiobiologically equivalent dose of 66Gy with inj.CDDP 40mg/m^2 weekly.

For other patients best supportive care was given.

RESULTS

The study group had 24 male and 6 female patients with median age of 56 years. Symptom relief of more than 50% noted in 80% of the patients with pain, 73% of the patients with dysphagia. Partial response rate after palliative

radiotherapy 76.6%. Grade 3 and grade 4 toxicity after palliative radiotherapy 0%. Patients eligible for further chemo radiotherapy at curative intent were 53%. 6 weeks after further chemo radiotherapy, 18.75% of the patients achieved complete response and 75% of the patients left with minimal residual disease.

DISCUSSION

There is paucity of guidelines with inadequate information on time dose fractionation, toxicity of such palliative regimens and QOL issues. Palliative radiotherapy (PRT) regimens should be tailored individually. As per guidelines more hypofractionated schedules can be used for end stage patients due to limited prognosis and survival. In this study, a short course of hypofractionated palliative radiotherapy 20 Gy (5 fractions, 4 Gy per fraction) provided appreciable symptom relief with manageable acute toxicity.

According to the guidelines, the treatment goal is cure even for advanced SCCHN with the intent of maximizing loco-regional control and achieving a potential cure. So this study offered further chemo radiotherapy at curative intent to good responders of palliative radiotherapy.

CONCLUSION

Short course hypofractionated radiation is effective for palliation to relieve the symptoms quickly with manageable acute side effects in advanced and unresectable head and neck cancers. This study reduce the economic

burden, treatment time, hospital stay and machine load. It also helps in selecting the patients for further chemo radiotherapy.

INTRODUCTION

Globally squamous cell carcinoma head and neck(SCCHN) accounts for 5.5 million cases every year. It is the 5th most common malignancy worldwide. About 300,000 head and neck cancer cases die annually, which reflects the burden of these cancers.[1.]

Two thirds of the new cancer cases diagnosed in the world are from developing countries like ours. High incidence of oral cavity cancers is reported from Australia, India, South Africa and Western Europe[2] Cancer incidence is highest in India among the SAARC countries[3].

Till date there is no single cause or mechanism responsible for causation of cancer in human beings. The incidence and prevalence of cancer in a geographical area is influenced by the specific environmental conditions existing there as well as the life style of that particular population. Hence the cancer trends vary from population to population. In India and other developing countries like South East Asia, some African countries and South America the incidence of HNC (Head and Neck Cancer) is high. Contrast to this, the incidence of head and neck cancers is very low in Northern Europe and USA.

INDIA

HNC is emerging as a major public health problem in India.

These cancers are mostly related to the life style of individuals and commonly occurs in 6th and 7th decade of life. Incidence of head and neck cancers in India is on rise because of the effective control of the infectious disease there by increased longevity of the population.

More than 200,000 cases of head and neck cancer are reported in India every year of which 80,000 cases are oral cavity cancers, 40000 cases are pharyngeal cancers excluding nasopharyngeal cancers and 29,000 cases are laryngeal cancers. Majority of these cases (60%-80%) in India are presented in advanced stage[4].

TAMIL NADU

As per Madras Metropolitan Tumor Registry (MMTR) data, most common cancer reported in men is HNC followed by stomach and lung. HNC is the 4th commonly occurred cancer in women. Government general hospital, Chennai has registered 17.8% of all cancers during the period 2006-2008. HNC cancers reported more commonly in men attributable to 25.62% as compared to 11.35% in women[5].

The total number of head and neck cancers registered in Barnard institute of radiology and oncology is 2032 cases in the year 2009, 1939 cases in the year 2010 and 2104 cases in the year 2011.It constitute 35 to 40% of all new cases

registered in a calendar year.65 to 75% of the patients were presented in advanced stages.

ETIOLOGY

Many etiological factors have been established in the development of SCCHN. Mainly,

1) tobacco in various forms,
2) consumption of alcohol,
3) betel nut chewing,
4) HPV infection (Human Papilloma Virus),
5) nutrional factors,
6) occupational exposure,
7) poor oral hygiene, ill fitting dentures and sharp teeth,
8) Immune suppression and genetic factors.

Smoking

Smoking was the first identified and established independent risk factor for oral, oropharyngeal and laryngeal cancers.[6.] In India, Tobacco used as smokeless (ghutka, as quid with beetel nut chewing, etc..) and smoke (ganja, beedies, cigars, pipes, etc..)form. All are responsible for the development of SCCHN. Beedi smoking is more hazardous as it is not filtered and the content

of tar, nicotine is more compared to manufactured cigarettes. Also they are smoked in different ways like reverse smoking which is more harmful. Tobacco contains almost 3800 chemicals of which 62 carcinogens have been identified.

Alcohol

Alcohol consumption also increases the risk of development of SCCHN. The quantity, frequency, type, duration of consumption have all been studied and implicated in the development of SCCHN.[7]

Tobacco smoking and alcohol together have synergistic and supra additive effect, with duration of consumption, amount, heavy and light smokers/drinkers, have all been shown to increase the risk of HNC especially oropharyngeal/laryngeal cancer[8]. Pooled analysis by International Head and Neck Cancer Epidemiology studied the population attributable risk (PAR) for SCCHN, concluded that PAR for tobacco or alcohol was 72% for HNC. Out of 72%, 33% was due to tobacco alone, 4% was due to alcohol alone, and 35% was due to combination of alcohol and tobacco[9].

Betel nut chewing

Betel quid is extensively used in India. It is also called as pan which is consists of pieces of areca nut, slaked lime and tobacco. Added to this are

spices, cardamom, cloves, according to the local preferences and are varyingly called as gutkha, zarda, mawa, khaini.

In India betel nut chewing, as quid with tobacco is most common risk factor for oral cavity cancer leading to premalignant lesions mainly sub mucosal fibrosis and invasive cancer at later date.

HPV

HPV has long been thought to play a role in some HNC. One study of more than 250 patients used PCR followed by definitive techniques such as sequencing and in situ hybridization to search for the presence of HPV in HNC[10]. It was seen in approximately 25% of the lesions, and virtually all were high-risk oncogenic types (HPV-16). Remarkably, more HPV-positivity was seen in the oro pharyngeal cancers. These HPV-positive oro pharyngeal cancers were least likely to occur among drinkers and heavy smokers ; least likely to harbor a p53 mutation, and had an improved disease-specific survival. Another group suggested that human papilloma virus positive cancers may also inactivate Rb gene, and harbor a better prognosis. These new data are consistent with previous studies of a smaller number of patients[11] or those that used less definitive techniques. It appears that Human papilloma virus positive

carcinomas of ororopharynx compose a distinct clinical and pathologic disease entity.

With the increasing incidence of oropharyngeal cancer in young patients who are never smokers/ alcoholics being established, it is attributed to increasing incidence of HPV infection; subtypes 16, 18. HPV-related HNSCC comprise about 25% of all HNSCC. 50% of oropharyngeal cancers and 0%-20% oral cavity cancers positive for HPV DNA[12.]

Genetic

In Fanconis Anemia, mutations of the genes like FAA, FAD and FCC will lead into the development of lymphoid malignancy and also the risk of development of second primary in tongue, Pyriform fossa and post cricoid region[13]

Bloom Syndrome patients who have mutations in helicase genes are predisposed to develop solid tumors, 6-8% of which arise in tongue and larynx respectively[14]

Homozygotes with ataxia telangiectasia who survive into their twenties and thirties are at higher risk of developing T cell Leukemia. Also these patients are at increased risk of developing carcinoma of the oral cavity, Stomach, Pancreas, Breast, Ovary and bladder[15]

Xeroderma pigmentosum manifests second primary in the oral cavity in addition to primary skin malignancies[14,16]

Cowden disease (PTEN), Multiple Endocrine Neoplasia type 1(MEN1) and type 2(MEN II), Neurofibromatis Type II (NF-2) and retinoblastoma (Rb) are some of the syndromes associated to primaries in head and neck.

Nutrition and Cancer

Vegetable consumption and fish in diet – found to be protective in a case control study in India on various head and neck cancers, with two fold higher risk of cancer in non-consumer.

Plummer vinson syndrome

It is characterized by Iron-deficiency anaemia, dysphagia and post-cricoid webs; associated with high risk of cancer oral cavity and esophagus.

PRECANCEROUS LESIONS:

Lichen planus (erosive form) oral submucosal fibrosis, leukoplakia and erythroplakia are known premalignant lesions in head and neck region.

Leukoplakia

Most common precancerous lesion is leukoplakia with rate of malignancy transformation from <1%-18%[17]. It is treated by excision.

Erythroplakia

Higher risk of malignant transformation than leukoplakia[18].

In histopathological examination, 51% of the erythroplakia patients was found to be invasive cancer;40% of the patients - carcinoma in situ; and 9% of the patients - mild or moderate dysplasia.

Submucosal fibrosis

Malignant transformation rare.

It is an important risk factor in the increase of oral cavity cancers in young individuals (< 35 years) in India.

ANATOMY

The commonly occurred malignances oh head and neck region are usually arising from oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and the paranasal sinuses. Malignances of thyroid gland, eye and brain are not included in the head and neck cancers. Although most of them consists of squamous cell carcinoma, there are many other histopathological diagnoses.

Oral cavity

The oral cavity contains the lip, floor of mouth, the anterior two third of tongue, buccal mucosa gingiva (upper and lower), hardpalate and retro molar trigone.

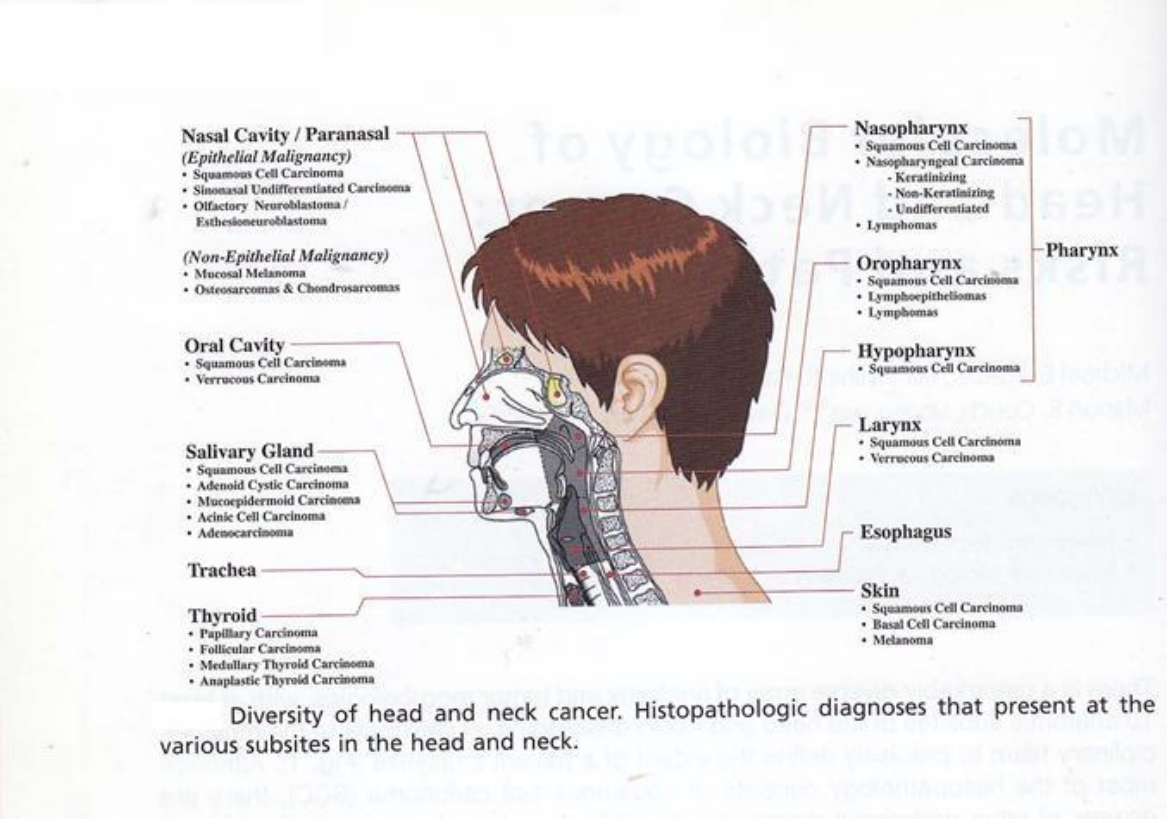
Lips

The lips are composed of the orbicularis oris. It covered by skin on its external surface and mucous membrane on its internal surface. The junction of skin and mucous membrane of the oral cavity is called the lip vermilion. The blood supply is by labial artery which is a branch of the facial artery. The motor nerve supply is by of the seventh cranial nerve branches. The sensory nerve supply to the upper lip is from the infraorbital branch of the maxillary nerve; and to the lower lip is by mental nerve.

Floor of mouth

The floor of mouth is a U-shaped structure bounded by the lower gum and the oral tongue; which terminates posteriorly at the insertion of the anterior

Figure -1; Head and neck anatomy



Diversity of head and neck cancer. Histopathologic diagnoses that present at the various subsites in the head and neck.

tonsillar pillar into the tongue. The two sublingual glands lie immediately below the mucous membrane; which is separated by the paired genioglossus and geniohyoid muscles. At the point of insertion of these two muscle groups at the symphysis are the bony protuberances, the genial tubercles which may interfere with the placement of interstitial sources. The mylohyoid muscle arises from the mylohyoid ridge of the mandible and is the muscular floor for the oral cavity. It ends posteriorly at the level of the third molar tooth. The submandibular gland

situated on the outer surface of the mylohyoid muscle between the mandible and the insertion of the mylohyoid muscle. Submandibular duct(Wharton's duct) is about five cm long. It lies between the sublingual gland and the genioglossus muscle. It opens in the anterior floor of the mouth close to the midline.

Anterior 2/3rdtongue

The circumvallate papillae is the landmark for the division between oral tongue and base of tongue. The arterial supply is mainly by paired lingual arteries. The sensory supply is by lingual nerve.

Buccal mucosa

Mucousmembrane covering the inner surface of lips and cheeks is called buccal mucosa; ends above and below with a transition to the gingiva. It extended posteriorly upto the retromolar trigone. The salivary duct opens into the buccal mucosa opposite the second upper molar is the parotid duct. It is innervated by a branch of the mandibular nerve , which is sensory supply to the buccal mucosa, and to the skin of the cheek.

Gingiva and hard palate:

The lower gingiva is the one which includes the mucosa covering the mandible from the gingivobuccal gutter and extends upto the origin of the mucosa on the floor of mouth. Retromolar trigone lying behind third molar and it is contiguous with the maxillary tuberosity above. The tendinous pterygomandibular raphe is present beneath the mucosa of the retromolar trigone, which is attached to the pterygoid hamulus and the posterior mylohyoid ridge of the mandible and is important in serving as the insertion of the buccinator, orbicular oris, and superior pharyngeal constrictor muscles. The pterygomandibular space lies behind the pterygomandibular raphe and between the medial pterygoid muscle and the ascending ramus. It contains the lingual and dental nerves. This space is related posteriorly tothe parapharyngeal spaceand the deep lobe of the parotid .minor salivary glands are absent in the mucous membranes of the alveolar ridges.

Oropharynx:

The oropharynx is the continuation of the oral cavity extends from the superior surface of soft palate to superior surface of the hyoid bone or vallecula. It contains base of tongue ,anterior surface of the soft palate and the uvula, the

tonsillar pillars- anterior and posterior. It also contains the glossotonsillar sulci, the pharyngeal tonsils, and the posterior and lateral pharyngeal walls.

Base of tongue

It is bounded anteriorly by circumvallate papillae, its lateral limit is the glossotonsillar sulci, and posterior limit is the epiglottis. The vallecula is a strip of mucosa that is in the transition from the base of the tongue to the epiglottis. But it is considered a part of the base of the tongue. The muscles of the base of tongue are continuous with the anterior two third of the tongue.

Tonsillar fossa

Its anterior limit is anterior tonsillar pillar, posterior limit is posterior tonsillar pillar.Inferiorly bounded by glossotonsillar sulcus and pharyngoepiglottic fold. Laterally the tonsillar region is bounded by the pharyngeal constrictor muscle and its fascia, the mandible, and the lateral pharyngeal space. Glossotonsillar sulcus separate it from base of tongue. Beneath the mucous membrane of the sulcus the styloglossal muscle and the stylohyoid ligament are present.

Soft palate

It is a thin, mobile muscle complex .The epithelium of oral side of the soft palate is squamous while the epithelium of the nasopharyngeal surface is respiratory type. It is continuous laterally with the tonsillar pillars.

Larynx

The larynx is composed of many cartilages connected by ligaments and muscles. It is divided on anatomic considerations into the supraglottic, glottic, and subglottic regions.

Supraglottis

Contains of the epiglottis (infra and supra hyoid), false vocal cords, ventricles, aryepiglottic folds and arytenoids. The arytenoids are cartilages which articulate on the cricoid.

Glottis

It contains true vocal cords and its anterior commissure.

Subglottis

The subglottis is 2 cm long . It extends from fivemillimetre below the free edge of true vocal cords to the upper margin of first tracheal ring. The preepiglottic space is a potential space bounded by the epiglottis posteriorly, the hyoepiglottic ligament and vallecula superiorly, and the thyroid cartilage and thyrohyoid membrane anteriorly and laterally. It can be seen as a low-density area on a computed tomography.

The supraglottic structures have a moderate to rich lymphatic supply. The lymphatic vessels pass via pre-epiglottic space and thyrohyoid membrane to the level II group. some trunks drain directly to level III or IV group.

Lymphatics capillaries are absent in the true vocal cords; hence, if any lymphnode spread from carcinoma glottis, is usually due to tumor extension to supraglottis or sub glottis.

The sub glottis has few lymphatic capillaries.

The lymphatic vessels pass via thyrocricoid membrane to pretracheal nodes in the region of isthmus of thyroid, or the trunks may drain into the level IV nodes. The pretracheal nodes are midline and, their salient feature is even when clinically positive, are 1 cm or less in diameter.

Posterior drainage of subglottis to the level IV nodes is through the cricotracheal membrane.

Hypopharynx

The epithelium of the pharyngeal mucous membrane is squamous and it is continuous with the nasopharyngeal mucous membrane. The dividing point between the nasopharynx and posterior pharyngeal wall is the Passavant's ridge. It is a musculature ring that contracts to close the nasopharynx during swallowing. The thin constrictor muscles of pharynx surround the posterior and lateral walls. Between the constrictor muscle and the prevertebral fascia, covering the longitudinal spine muscles (longus colli and longus capitis) is the retropharyngeal space which is a thin layer of loose areolar tissue. The thickness of posterior pharyngeal wall is notmore than one cm in the midline, (from its mucous membrane to the anterior vertebral body). Lateral to the pharyngeal wall there lies vessels, nerves, and muscles of the parapharyngeal space. The constrictor muscles are relatively thin, especially the superior constrictor, and do not present much of an obstacle to tumor penetration. There is a variable weak spot in the lateral pharyngeal wall which lies just below the hyoid; in this region the middle and the inferior constrictor muscles fail to overlap. The lateral wall in this area is composed of the thin thyrohyoid membrane, which is useful for the penetration by the vessels, nerves, and lymphatics of the

laryngopharynx. The pharyngeal walls are continuous with the cervical esophagus below, at the level of upper esophageal sphincter; the transition to cervical esophagus is below the arytenoids (C4). The transition zone, 3 to 4 cm in length, is the postcricoid pharynx.

The lateral pharyngeal wall is a narrow strip of mucosa that lies behind the posterior tonsillar pillar in the oropharynx, and then continues down into the hypopharynx. Here it forms the lateral wall of the pyriform fossa. Posterior cornu of the hyoid bone occasionally protrudes into the lateral pharyngeal wall on one or both sides, to produce a submucosal bulge.

The pyriform fossa is made up of three walls: the anterior, medial, and lateral (there is no posterior wall). The pyriform sinus tapers inferiorly to the apex and usually terminates variably at a level between the superior and inferior borders of the cricoid cartilage. Superior limit of pyriform sinus is opposite the hyoid. The thyrohyoid membrane is lateral to the upper portion of the pyriform sinus, and the thyroid cartilage, cricothyroid membrane, and cricoid cartilage are lateral to the lower portion. Superiorlaryngeal nerve (internal branch), a branch of vagus, lies under the mucous membrane on the anterolateral wall of the pyriform fossa. The auricular branch is sensory to the skin of back of the pinna and the posterior wall of the external auditory canal.

The postcricoid pharynx is funnel shaped to direct food into the gullet. The superior margin begins just below the arytenoids. The anterior wall lies behind the cricoid cartilage and is the posterior wall of lower larynx. The posterior wall is a continuation of hypopharyngeal walls. Recurrent laryngeal nerve lies between the lateral wall and the deep surface of the thyroid gland.

PATHOLOGY

Most of the head and neck malignant neoplasms arise from the epithelium and are squamous cell carcinoma. Other varieties of it are lymphoepithelioma, spindle cell and verrucous carcinoma.

Among HNC more than 90% of are squamous cell carcinoma. There are three Histological grades are classified on the basis of Keratinisation.

Well differentiated- more than 75% of Keratinisation,

Moderately differentiated - 25 to 50% of keratinisation

Poorly differentiated-less than 25% of keratinisation.

In general, poorly differentiated cancers are more prone for the regional metastases, so prognosis is poor. Pathological grade is not a consistent predictor of prognosis. Features that predict aggressive behaviour and poor prognosis

include perineural spread, lymphatic invasion and extracapsular extension(ECE) of lymphnode.

Morphologically, four types of growth patterns are recognized.

Ulcerative

It is the most commonly occurred type. It is oval or round ulcer that is friable in nature.

Infiltrative

Ulcerative lesions extending deeply into underlying tissues and become as an infiltrative growth.

Exophytic

It usually grow superficially and metastases occur at later stages when compared to the other types. It looks like an area of thickened epithelium.

Verrucous cancer

It is a rare variety, commonly occurs in older age group. Its occurrence is associated with poor oral hygiene and ill-fitting dentures. It is bulky, warty and raised fungating lesion. It never give rise to metastases.

Other tumor types

Other less common head and neck cancers are mucoepidermoid carcinoma,

adenoid cystic carcinoma

adeno carcinoma

small cell undifferentiated cancer

Esthesio neuroblastoma (olfactory neuroblastoma).

Sarcoma

Melanoma

Lympho epithelioma

Hodgkin's lymphoma and nonhodgkin's lymphoma of lympnodes of the neck and Waldeyar ring.

FIELD CANCERISATION

HNC patients often present with metachronous or synchronous second primary of aerodigestive tract. Patients with primary cancer may have skip lesion which are characterized by pre invasive lesions throughout the field due to chronic exposure of carcinogenic agents clinically. Slaughter et al attributed

this to a field defect that allowed independent transformation of epithelial cells at a number of sites. Then these tumors grew by its own, with genetic alterations. For HNC, the working progression model of author allowed direct assessment of the genetic alteration in surrounding areas of abnormality. In all cases, surrounding lesions have the same genetic events of the primary tumor. It suggests that independent and geographically distinct skip areas are mainly due to single transformed cell. It is observed that a cell is transformed by a critical genetic event and begins to migrate through the normal mucosa. Additional genetic events in one critical lesion eventually give rise to the clinical tumor that is seen on presentation. However, direct molecular assessment of surrounding regions confirms the presence of clonal cell populations that are not yet fully transformed. Given time, these lesions arise as other pre invasive or invasive lesions in the same patient.

Grades

Histologically graded into four types

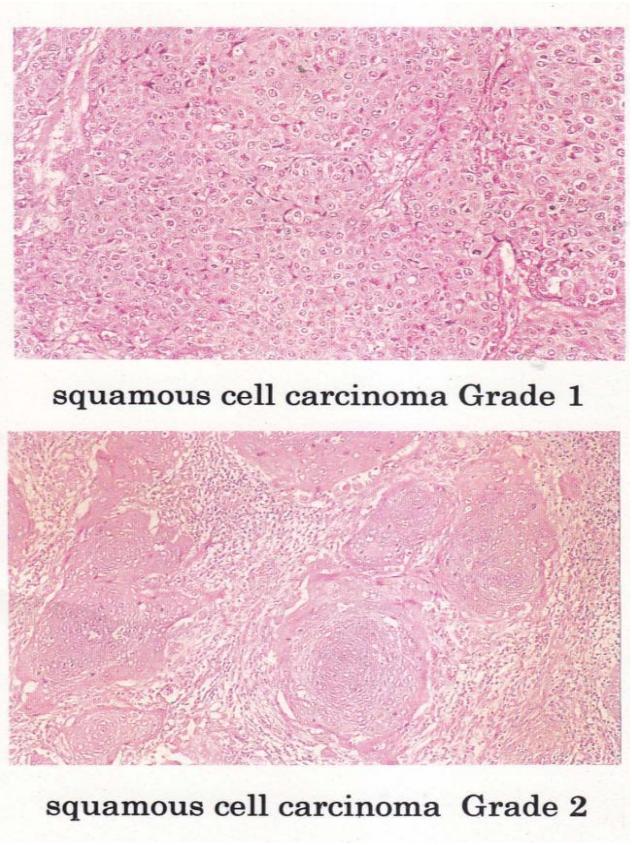
Grade 1: well differentiation

Grade 2: moderately differentiation

Grade 3: poorly differentiation

Grade 4: undifferentiation

Figure – 2 Grade 1 and 2 squamous cell carcinoma



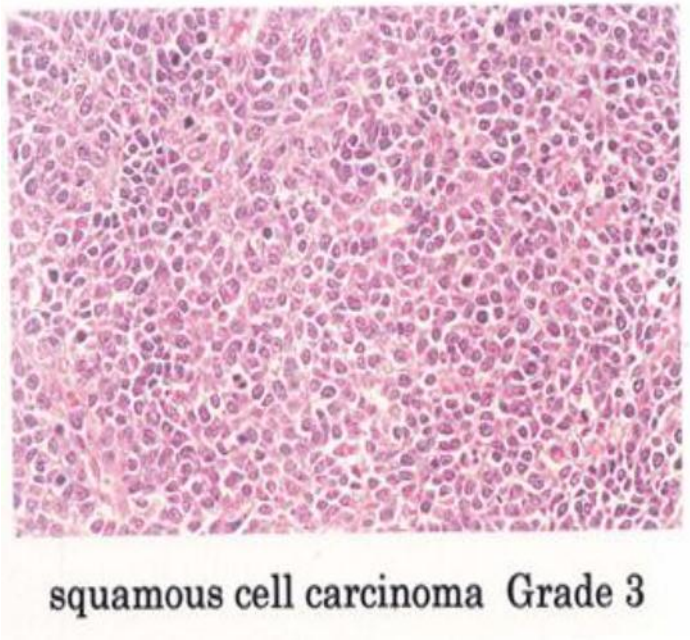
PATTERNS OF SPREAD

Spread is dictated by local anatomy and varies by each anatomical site. By direct spread muscle is invaded and spread along the fascial planes to involve adjacent soft tissue structures also occurred.

Tumor may attach to periosteum or perichondrium but involvement of bone and cartilage is a late event. Bone or cartilage act as barriers to spread and its invasion is indicative of a biologic aggressiveness of SCCHN. Slow growing

neoplasms of the oral cavity may produce a smooth pressure defect of the underlying bone without actual bony erosion.

Figure – 3 Grade 3 squamous cell carcinoma



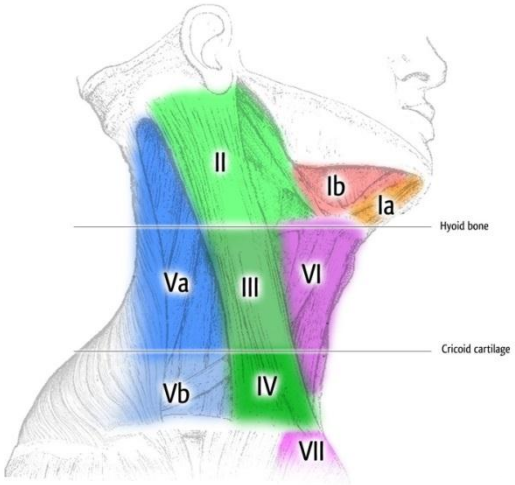
Spread of tumor into space allows superior or inferior spread from base of skull to lower neck.

Perineural spread is observed in muco epidermoid carcinoma which predicts a poor locoregional control rate . Tumors with perineural spread may track along the nerve to base of skull, central nervous system and also peripherally which may lead to neurological symptoms.

Invasion of the vascular space leading to the development of regional and distant metastases.

Lymphatic spread

Figure -4



Lymph node levels

Lymphatic involvement depends on the staging, histology, grade and site of the tumor and also the presence of vascular space invasion and the density of lymphatics.

By studying the occurrence of node positive cases by elective neck dissection or by determining the probability of regional recurrence, the risk of sub clinical disease in a clinically negative neck can be obtained. The relative incidence of clinically positive nodes determined by anatomic site of primary and T stage. Well lateralized lesion will spreads to ipsilateral neck. Midline lesions spread to both side;carcinoma of tongue base and nasopharynx will involve both sides of neck even when it is situated well laterally

Table – 1 Lymphatic drainage of neck

Ia	Submental group
Ib	Submandibular group
II	Upper cervical group
III	Mid cervical group
IV	Lower cervical group (transverse cervical)
V	Spinal accessory chain lymph nodes
VI	Prelaryngeal, pretracheal, paratracheal group

Patients with large or multiple clinically positive ipsilateral nodes are at risk of developing contralateral disease.

Disturbance and obstruction of the lymphatic pathways by surgery or Radiotherapy shunts the lymphatic flow to the opposite side. Contralateral

metastases from a well lateralized lesions most commonly involves the level II node; sometimes may be bypassed the level II and involves level III or level IV.

The incidence of retropharyngeal adenopathy is based on the primary site and presence of clinically involved nodes.

Involvement of lymph node levels are predictive of the primary site. Lip and oral cavity tumors spread to level I initially. Larynx and pharyngeal cancers involves levels II and III.

Distant spread:(haematogenous spread)

Risk of distant metastases are related to neck stage(N stage) ,lymph node location and site of primary. Risk is less than 10% for N0 or N1 neck and 30% for N3 and N1 or N2 below thyroid notch. Hypopharynx and oropharynx carcinomas give distant metastases more commonly than oral cavity.

Lung is the commonly involving organ in metastatic SCCHN (50%)

HISTORY AND DIAGNOSTIC WORK -UP

Detailed clinical history of the patient including the history of usage of tobacco, alcohol, oral sex, and other environmental exposures which are mentioned in etiological risk factors should be taken. Patient with symptoms

suggestive of malignancy of upper aerodigestive tract of more than two weeks duration or with an asymptomatic neck mass should be evaluated further carefully.

PHYSICAL EXAMINATION

Thorough physical examination can find even the early lesions of the aerodigestive tract and also the multiple primaries which are common in upper aerodigestive tract. This will also indicate the severity and the duration of the disease.

Physical examination should be done in a systematic manner so that any point is not going to be missed. Frequently overlooked part of the examination like searching for ulcers, nodules, pigmented and other suspected lesions should be done carefully.

Cranial nerve examination is must for all patients of head and neck tumor or mass. Any discharge, bleeding and drainage from eyes, nose and ear to be looked for.

Examination of the oral cavity should be done completely. Looking for halitosis and Trismus is must. Bimanual palpation of the floor of mouth, tongue, buccal mucosa should be done with one finger inside the mouth and other outside the mouth. Mandible is to be palpated for involvement; any tenderness,

thickening, discharge, sinuses etc to be noted and biopsy of the suspected lesion is to be taken.

Nose

External nose, anterior nares, alae and vestibule should be carefully examined.

Neck

Neck examination is to be done systematically to look for the location of any mass. Neck examination should be done by inspection, palpation, percussion and Auscultation. Palpation is an important step in the examination of neck. Mass and the nodes are palpated between the thumb and index or middle finger.

The location, size, consistency, fixity and tenderness of the node to be examined.

Posterior Rhinoscopy:-To see choane, entire nasopharynx .

Anterior rhinoscopy:-To see the vestibule, nasal septum, lateral wall and floor of the nasal cavity.

Indirect Laryngoscopy: For examining the Base of the tongue, Vallecula, hypopharynx and the larynx. Inspection and mobility of the vocal cords is to be

evaluated. This provides an overall picture of the mobility and asymmetry indicating the presence of an occult tumor.

Direct Laryngoscope:-Thorough visualization of the nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx can be done and pooling of secretions to be noted. Individual subsites also to be looked into for any doubtful lesions.

Endoscopy:-Because of the field cancerisation patient with Head and neck malignancy will have a 5% of chance of Synchronous primary that is SCCHN, lung or oesophagus. Laryngoscopy(direct), oesophagoscopy and bronchoscopy (Triple endoscopy) to be done in all patients with an unknown primary and in a known primary of HNC and doubtful lesions are biopsied. These can also provide details about the extension of disease.

DIAGNOSTIC IMAGING

Chest X-ray – to see for any pulmonary metastases or a second primary.

Orthopantomogram

To look for involvement of bone in oral cavity lesion.

USG

Ultra Sound scan is not of much use in the management of SCCHN.

CT Scan

It delineates the extent of the tumor(both primary and secondary) and can differentiate the solid from cystic lesion.

The site of an unknown primary with secondary neck node can be identified by CT scans of chest, abdomen and pelvis. It has advantage over MRI in detecting bony erosions. With its high spatial resolution fat, muscle, bone and other soft tissues are easily identified.

Dynamic contrast CT[DCC]

With the use of less contrast agent, it able to differentiate blood vessels from malignant mass and lymph nodes.

Spiral CT

Faster than DCC and it has the capacity for multiplannar reconstruction without compromising on the quality of scan.

MRI

It gives information about the size, location and the extent of the tumor accurately. Gardolinium enhanced MRI is very useful than CT for imaging nasopharyngeal and oropharyngeal carcinoma.

Main disadvantage is movement artifact particularly in larynx and hypopharyngeal carcinomas.

STAGING

The staging for the primary lesions (T) is done by using The American Joint Committee on Cancer (AJCC) (2010). The AJCC (2010) neck staging (N) is common to all head and neck sites, except the nasopharynx[19].

T staging is done purely depending on the individual site.

But N staging remains common for all.

N staging of HNC

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm

or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node

More than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest

dimension or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N2a Metastasis in a single ipsilateral lymph node,

more than 3 cm but not more than 6 cm in greatest dimension.

N2b Metastasis in multiple ipsilateral lymph nodes,

none more than 6 cm in greatest dimension.

N2c Metastasis in bilateral or contralateral lymph nodes,

none more than 6 cm in greatest dimension.

N3 Metastasis in a lymph node, more than 6 cm in

greatest dimension.

TREATMENT OVERVIEW

For practical purposes, SCCHN can be divided into 3 clinical stages:

1) early disease
2) locoregionally advanced disease
3) Metastatic/recurrent disease.

Of these 50-60% is locally advanced atpresentation.

Treatment approaches for each stage vary.

EARLY STAGE DISEASE

Usually single modality treatment with either Surgery or Radiotherapy provides comparable and efficacious locoregional control and survival results.

Surgery

Surgical resectability of a head and neck cancer is assessed by a multidisciplinary team. An adequate margin of 1.5 cm to 2cm is required to obtain a clear frozen section. Any suspected margin of < 2 cm has to be examined by a frozen section. A clear margin is defined as a distance of ≥ 5 mm from the resected margin to the invasive tumor. A close margin is a distance of < 5 mm. Primary is usually approached through a trans oral, transcervical or, through mandibulectomy.

Reconstruction is done by using skin graft, free tissue transfer, regional flap, or by primary closure. Reconstructed area should functionally and cosmetically resemble the resected tissue.

Neck dissection:

Elective neck dissection is done in clinically node negative neck. Therapeutic neck dissection is done in clinically apparent nodal disease. Based on the clinical, radiological and preoperative finding, therapeutic dissections

may be either selective or a comprehensive neck dissection. Tumors approaching midline or tumors with bilateral lymphatic drainage like base of tongue, palate, and supraglottis should undergo dissection in both sides of neck.

Radiotherapy:

Primary disease and involved neck nodes are to be treated by 66 to 70 Gy of radiotherapy in conventional 2 Gy fractions. Low to intermediate risk lymph nodes are to be treated electively between 44 and 60 Gy. Advanced tumor stage, depth of invasion, perineural invasion, multiple node positivity, vascular invasion and lymphatic invasion require postoperative radiotherapy. Post operative chemo radiotherapy is indicated when there is extra capsular extension and positive margins. Postoperative radiotherapy is usually administered in 6 weeks or less. Radiation may be delivered either in conventional or altered fractionation.

Surgery vs radiotherapy

The advantages of surgery over radiotherapy are one time procedure, limited amount of tissue is exposed to treatment and shorter hospital stay.

Also disadvantage of radiation like acute and late toxicity can be avoided and radiation can be reserved for salvage purposes and second primaries. The advantage of radiation therapy is organ preservation and thereby function preservation.

LOCOREGIONALLY ADVANCED CANCERS

Aggressive multimodality treatment is needed to achieve cure in these patients. Therapy for locally advanced SCCHN has the major goals of eradicating locoregional disease, treating distant micrometastases, preserving organ function, and minimizing toxicities.

In the past, 5 year survival for loco regionally advanced cancer was only forty percent. (ten to thirty percent for patients with stage IVa and IVb tumors). Most of the patients developed recurrence due to loco regional failure. More than fifty percent of patients who die from HNC have locoregional disease as the only site of failure, and almost 90% of patients with distant failure also have persistent locoregional disease. Therefore, the efficacy of any curative approach is measured by its ability to achieve locoregional control[20]. Historically, locoregionally advanced tumors were treated with surgery (with or with out adjuvant radiotherapy) or radiotherapy alone. Small amount of patients only had an adequate surgical resection, and the outcomes were poor with respect to

survival and organ preservation. Furthermore, radiotherapy alone is not sufficient to successfully treat most HNC at locoregionally advanced stages. Altered fractionation schedules have also been studied clinically. Even the most effective RT regimens result in local control rates of 50% to 70% and Disease Free Survival (DFS) of 30% to 40% [21].

Hence multimodality treatment is necessary to achieve good locoregional control. 50% to 60% of locoregionally advanced cancer patients develop locoregional recurrence within two years even after surgery, radiotherapy, or both and 20% - 30% of patients landed in distant metastases. So chemotherapy was investigated to maximize the response along with Radiotherapy – as induction, concurrent and adjuvant chemotherapy[21].

Induction chemotherapy

Overall response rate of induction chemotherapy using cisplatin and 5Fu that shown in various trials is 60 complete response rate is 20 to 30%. It also decreased the occurrence of distant metastasis because of the early effect on micro metastasis in the circulation. But induction chemotherapy failed to showany survival benefit. The recent phase III randomised trial (DeCIDE trial) which using docetaxel, cisplatin and 5FU as a induction chemotherapy followed

by concurrent chemo radiation also failed to show any survival benefit when compared to concurrent chemo radiation [22].

Concurrent chemo radiation

Concurrent chemoirradiation has shown clinically significant benefit with better locoregional control as well as survival benefit. During the past 2 decades definitive concurrent chemoirradiation has shown to improve survival and organ preservation in locally advanced Head and Neck Cancer [23].Recent meta-analysis reveals an survival benefit (absolute) of 4.5% for chemoirradiation (neoadjuvant, concurrent, adjuvant chemoradiation) in SCCHN, and 6.5% for concurrent chemoradiation over RT alone [24]. The advantage of the adding chemotherapyto historical treatment is same in all sub sites of SCCHN[25]. Concurrent platinum based chemoradiation regimens have demonstrated improved disease control rates compared to those obtained using radiotherapy alone and is the most commonly used chemotherapeutic agent in clinical use [24], with manageable toxicity. So at present the standard of care in patients with locally advanced and unresectable head and neck cancer is concurrent chemo radiation using Single agent high dose cisplatin.

Increased toxicity is noticed in combination chemotherapy group. The purpose of adding chemotherapy to radiation is to enhance the effect of

radiation. So it is important to complete the radiation therapy within the scheduled time. It is not good to interrupt radiation in between because of acute toxicity of combination chemotherapeutic agents. So single agent chemotherapy is preferred.

Adjuvant chemotherapy

The use of adjuvant chemotherapy has a theoretical benefit of eradicating the sub clinical disease left behind after chemo radiation. The increased sensitivity of minimal residual disease to anticancer drugs has been shown by cell cycle and growth fraction studies. It is also postulated that adjuvant chemotherapy sterilizes the micro metastasis present in the circulation and thereby prevent distal recurrence rate and improve overall survival rate. Unfortunately these theoretical benefits are not proved by any randomised control trials. So its use is far from definitive.

PALLIATION

But in the developing country like India, majority of the locally advanced HNC patients are often found unfit for radical combined modality treatment due to poor nutritional status and poor general condition. These patients need palliative anti cancer therapy and/or best supportive care(BSC).

PALLIATIVE RADIOTHERAPY (PRT)

Palliative radiotherapy (PRT) offered, effective palliation and improved the quality-of-life in advanced and unresectable SCCHN[26] and accounts for a significant amount of cancer care across the world. However, studies are very minimal about Palliative radiotherapy in HNC. Poor compliance to therapy and limited inclusion in prospective trials render outcome assessment difficult and challenging in these patients. Furthermore, limitation in resources both in terms of personnel and radiation equipment in developing countries like India has led to a situation where timely delivery of PRT to patients with short life expectancy is compromised. An expert panel had earlier concluded that insufficient information precludes estimations of the frequency, degree of or duration of symptomatic relief from PRT of HNC[27].There is no general consensus in the current literature regarding the optimal choice of palliative regimens for these patients. There is paucity of guidelines with inadequate information on time dose fractionation, toxicity of such palliative regimens and QOL issues. PRT regimens should be tailored individually. Severe toxicities due to radiotherapy should be avoided when treatment is for palliation.

Recommended PRT schedules are the following

50 Gy in 20 # (fractions)

30 Gy in 10 #

30 Gy in 5 #

60 Gy in 30 #

37.5 Gy in 15 #

More hypofractionated schedule can be used for end stage patients due to limited prognosis and survival.

SELECTION OF PATIENTS FOR PALLIATIVE INTENT TREATMENT

According to the guidelines, the treatment goal is cure even for advanced SCCHN with the intent of maximizing loco-regional control and achieving a potential cure. So it is hard to find the exact patients with advanced disease eligible for palliative treatment alone as compared to those in whom radical intent treatment could still be considered.

The following factors can guide the oncologist about patients selection for palliative intent treatment alone.

1) fixed, unresectable and inoperable tumors (primary and secondary)

2) very advanced, incurable loco-regional cancer with poorgeneral condition and medical comorbidities;

3) metastatic disease and patients with limited expected survival.

BEST SUPPORTIVE CARE

Best supportive care includes

1) Management of pain and vomiting
2) Management of anemia due to cancer and cancer treatment
3) Management of fatigue due to cancer
4) Management of distress due to symptoms.
5) Prevention and treatment of infections due to cancer.
6) Palliative care and nutrition support.

PROGNOSTIC FACTORS

Neck node involvement is the single most important factor in determining the survival of a HNC (beside tumor status).

Neck node involvement reduces the 5 year survival rate by 50%.

Nodal size (N2 or N3) and extra capsular extension are distinct prognostic features. The risk of neck failure and poor survival are fairly high.

Multiple lymph node involvement or contralateral nodal metastasis denote a poor treatment outcome.

LITERATURE

REVIEW

LITERATURE REVIEW

VERY ADVANCED HEAD AND NECK DISEASE

Very advanced head and neck diseases are following

1)Newly diagnosed locally advanced disease

2)Unresectable nodal disease which is newly diagnosed

3)Persistent or recurrent tumors

4)Metastatic disease

5)Patients not suitable for surgery.

Treatment option for these advanced and unresectable cases is mainly based on the Eastern Cooperative Oncology Group(ECOG) Status. For ECOG 1 and 2 patients, concurrent chemoradiation can be given. Palliative RT or best supportive care is the option for patients with ECOG 3.

Previous Palliative radiotherapy trials

Best supportive care alone is shown a median survival of 3 to 6 months in advanced Squamous cell carcinoma of head and neck[28]. In one of the largest studies[29] on the natural history of untreated HNC, 808 patients were followed-

up until their death. All the patients were given best supportive care, but specific cancer treatment was not done due to advanced disease status, poor PS or patient refusal to the treatment. The median overall survival was 100 days ranged from 1 day to 53.8 months. PS was the only predictor of survival ($P<0.001$) on multivariate analysis. 50% of untreated patients died within 4 months of diagnosis, but a small subset of patients with low tumor burden and good PS (performance status) survived upto 4 years. It has been concluded and argued that PRT neither improves survival, nor positively impacts on QOL of patients with SCCHN.

Burns et al [30] conducted a study on 76 patients with advanced cancers of the upper aero-digestive tract with radical or palliative intent. Clinical stage, tumor site and performance status were important prognostic factors. Overall mean survival was 15 months with a 2-year disease-free survival of 16%. Patients treated with radical approach had a mean survival and 2-year disease-free survival of 19.4 months and 29% respectively. On the other hand, palliative intent treatment was associated with a mean survival of 8.4 months and virtually there were no long-term survivors. Appreciable palliation was achieved in 25% of patients , but the remaining patients continued to have pain, significant distressing symptoms related to speech and swallowing. The results of palliative intent treatment was not better than best supportive care leading the

authors to conclude that there is small benefit associated with palliative treatment in SCCHN.

There is no high level evidence regarding the use of palliative head and neck radiotherapy, but several retrospective studies[31.32.33] case-control studies [34,35] single arm prospective studies[36,37,38,39,40] and one small randomized controlled trial [41.] confirms that palliative treatment is associated with an improved outcome.

In a retrospective study,[31] 40 cases of unknown primary with advanced neck nodes were treated with 30 Gray in 10 fractions over 2 weeks and 20 Gray in 2 fractions with one week break in between. There was a good one year response rate (77% and 48% respectively), with a similar symptomatic response rate of 68% and 38% respectively.

Lusinchi et al [32] studied 54 patients with palliative radiotherapy(30 Gy/15 fractions/3 weeks). Good responders were taken up for further radiotherapy of curative doses with or without treatment breaks. Radiotherapy was discontinued in 18/54 (33%) patients even before the planned 30 Gy due to poor PS, intolerance to Palliative radiotherapy, progression of disease and

logistical reasons. Local control rate at 3 years was 19%. The 2 year overall survival and 5 year overall survival for patients received Palliative radiation was 16% and 5% respectively.

Cyclical accelerated split course radiotherapy with concurrent chemotherapy was offered to 34 patients with advanced unresectable SCCHN[34].Radiotherapy dose was 23.4 Gray in 9 days divided into 1.8 Gy, two times daily for a total tumor dose of 70.2 Gray in 3 cycles (51 days). The two year local control and survival was 81% and 58% respectively. Excellent palliation was achieved with acceptable overall toxicity. This result was comparable to historical controls treated with palliative radiotherapy.

Carvalho et al [35.]compared patients with advanced HNC who received treatment with those who remained untreated until death having the same demographic and clinical characteristics. They found a significant difference between the survival rates of the untreated group and those of the treated groups that was independent of the type of treatment performed ($P< 0.00001$) or the tumor response to treatment ($P < 0.0001$).

Paris et al[36] conducted a study which has given fractionationated radiotherapy of 370 cGy per fraction given daily 2 times for 2 days, totally 4 fractions. It was repeated every three to four weeks giving a total dose of 44 Gray in 9 weeks. Good palliation was achieved in 33 (84.6%) of 39 lesions in 37 patients with minimal acute toxicity. The mean survival was 4.5 months ranged from 2 weeks to 31 months.

Minatel et al [37.]conducted a study on 58 patients with split course radiotherapy, 50 Gy in 20 fractions with a treatment gap of two weeks after the first 25 Gy with concurrent chemotherapy bleomycin. Study result was 69% local control rate with median response of 7 months. Symptom relief was observed in 81% of patients, but there was increased grade 3 toxicity(79%).

25 advanced SCCHN patients were given short course Palliative radiotherapy of 30 Gy in 10 fractions over 2 weeks[38.] Baseline symptoms were assessed with an 11-point numerical .At 1-month after PRT , all 22 patients with pain and more than 90% of the patients with swallowing difficulty, respiratory distress and insomnia showed>50% symptomatic relief. Cough was relieved in 60% patients. The median duration of symptom relief was 3 months. No grade 3 toxicity was noted.

The QUAD SHOT [40] delivered 14 Gy in 4 #, two times daily with 6 hours gap period for two consecutive days. Then the same schedule was again given at four weekly interval for a further two courses, if there was no tumor progression. Like that maximum cumulative dose of 42 Gray in 12 # was given. 16 patients (53%) had an objective response and 7 patients had shown static response. Median overall survival was 5.7 months ranged from 0.6 to 26.7 months, with a median progression-free survival of 3.1 months ranged from 0.6 to 11.4 months. Grade 3 toxicity was nil. Patients were asked to rate their quality of and to comment whether they thought radiotherapy was useful. Performance status was improved in 67% of the patients. All patients were tolerated the radiotherapy well and QOL was improved in 11 of 25 (44%) patients. Treatment was thought to be worthwhile by 43%, 58% and 63% of patients after first, second and third courses of cyclical radiotherapy respectively.

So what is the optimum dose-fractionation schedule?

In the last decade or so, there were lot of clinical trials established that short course PRT was effective in incurable solid tumors like bone metastases,[26] brain metastases [(26a)] and lung cancer [(26b)]. But there was no such trials for palliative radiotherapy in advanced and incurable SCCHN. It has been

a argument that a higher total dose is needed for growth restraint and durable palliation in HNC. Various dose-fractionation schedules that have been used in the above mentioned sites have been extrapolated for use in HNC palliative radiotherapy. Although the quality of evidence is not very clear, the weight of evidence favours a short course fractionated regimen like 20 Gy in 5 fractions or 30 Gy in 10 fractions as compared to single fraction or protracted courses of palliative radiotherapy.

SELECTION OF PATIENTS FOR FURTHER RADIOTHERAPY (DOSE ESCALATION)

Good responders to PRT have traditionally been treated with further radiotherapy of curative doses[39.]

Mohanti et al [39]conducted a study on 505 stage IV SCCHN patients. All patients were given a dose of 20 Gy , 4 Gy/#, total 5 fractions over one week. Seventy percent of patients presented with two or more distressing symptoms. On assessment at one month post PRT189 patients(37%) attained a partial response and had became ambulatory. These patients were well suited for further radiotherapy. Good symptomatic relief (50% or more) was observed in 57% for pain, 53% for swallowing difficulty, 57% for voice change, 47% for ear pain, 76% for dyspnoea and 59% for cough. The main acute toxicity of PRT

was grade 2 mucositis and dermatitis. Median overall survival with palliative radiotherapy was 200 days. The 153 patients were received further radiotherapy with curative intent had a significantly better overall survival of 400 days.

Rajan Paliwal et[42].al treated 50 stage 4 disease SCCHN patients with a total dose of 20 Gy,4 Gy per fraction, total of 5 fractions. Majority of patients (60-70 %) had symptom relief of more than 50%. Further radiotherapy was given according to tumor regression status of the patients.

A study conducted by Agarwal et al [43]where palliative radiation 40 Gy in 16 # in 3½ weeks was given. Disease regressed patients with acceptable acute toxicity were received dose escalated radiotherapy up to a maximum dose of 50 Gray. Complete response was seen in10 percent of the patients; while partial response was seen in 63% of the patients after 6 to 8 weeks of completion of radiotherapy. progression free survival at 1 year was 55.1%. At completion of radiotherapy a 57% of patients showed 50% to 75% of symptom relief while 17% showed more than 75% symptom improvement as compared to baseline in symptoms like pain, swallowing difficulty , and voice change. However this study results in grade 3 mucositis and grade 2 xerostomia in more than 50% of the patients.

Ali My et al [44] conducted a study comprising 30 locally advanced SCCHN patients who were treated initially by palliative radiotherapy 30 Gy in 3 Gy per fractions. Patients attaining more than 50% symptomatic relief and partial response at primary and nodal site and in good general condition after one month of palliative radiotherapy were taken up for further radiotherapy with curative intent. Further radiotherapy was given in 2 Gray per fractions upto a total radiobiologically equivalent dose of 66 Gray with same radiation portals that were used in PRT. Spinal cord shielding was done at 40 Gy. Further dose was calculated by Time-Dose-Fractionation (TDF) method taking into account the dose fraction of palliative radiotherapy with gap correction.

TUMOR REPOPULATION DUE TO TIME INTERVAL GIVEN FOR DOSE ESCALATION

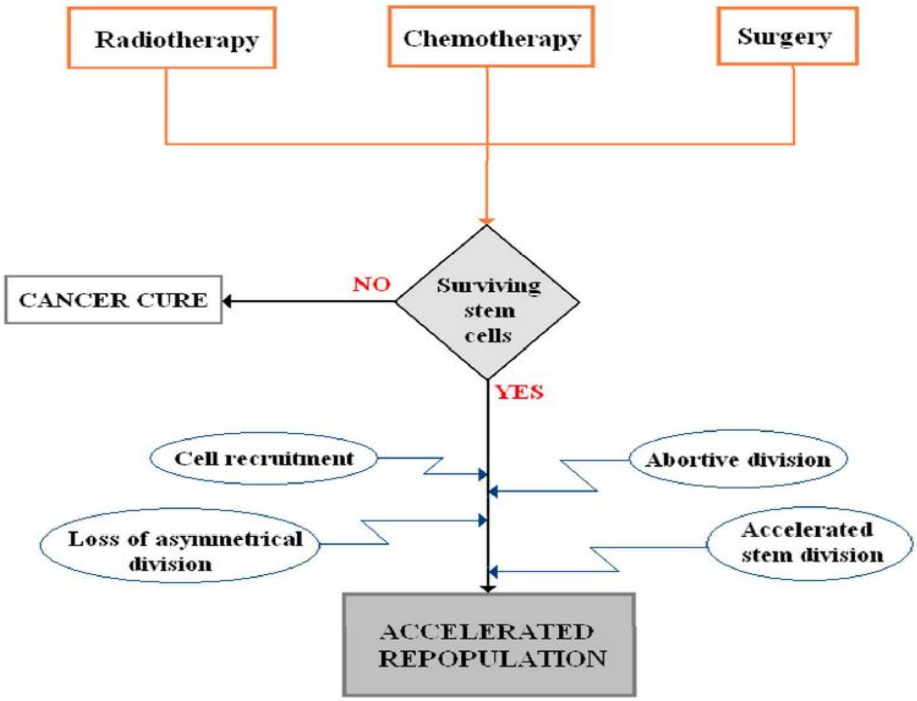
In locally advanced SCCHN, inferior clinical results with radiotherapy and chemotherapy is due to accelerated repopulation of the cancerous cells [45]. Cytotoxic injury to squamous cancer cells respond by increased mitotic rate as happened in normal cells since these cells retain some homeostatic control [45].Tumour repopulation mechanisms are similar to normal tissue repopulation.

Prolongation of treatment time results in repopulation of stem cells which are surviving the treatment.

Tumour repopulation mechanisms:

Locally advanced SCCHN tumours respond to cytotoxic effect of radiotherapy and chemotherapy by increasing the mitosis of surviving stem cells.

Cell recruitment – from pool of quiescent cells.



Three A's of repopulation:

- Stem cell division acceleration.
- Abortive division.
- Asymmetrical loss in stem cell division

Single agent chemo vs Combination chemotherapy

Concurrent chemoradiation can be given by using single or multiple agents of chemotherapy with radiotherapy. The single agent mitomycin C- bio reductive alkylating agent, has been studied extensively. Mitomycin is cytotoxic agent which is active against hypoxic cells thereby increase the therapeutic ratio. The other single agent chemotherapy drugs usedfor concurrent chemo radiation are cisplatin, 5-flurouracil and methotrexate.

Because, initial trials with single agent chemotherapy plus radiotherapy showed improved loco regional control and overall survival, people started using combination chemotherapy concurrently with radiation. The combination of cytotoxic drugs like cisplatin and 5 fluorouracil is highly active against squamous cell carcinoma of head and neck. But more toxicity was occurred while using combination chemotherapy concurrently with radiation and it required more supportive care.

Because of increased toxicity in combination chemotherapy, it is not advisable in a setting where intensive supportive care cannot be provided. The purpose of giving chemotherapy concurrently with radiation is to enhance the radiation effect. So it is important to complete the radiation therapy within the prescribed time. Also It is not good to interrupt the radiation in between due to increased acute toxicity of combination chemotherapy drugs. Hence, concurrent use of single agent cisplatin along with radiation is the standard of care for SCCHN.

Three weekly chemo vs Weekly chemo

The dose of single agent cisplatin is 100 mg/$m^2$of body surface area every three weekly. There is increased toxicity like mucositis, vomiting and renal toxicity noted with this three weekly dose of cisplatin. This needs more intensive supportive care and more resource implications. This also results in frequent interruption of treatment and poor patients compliance. Therefore it is logical to give the cisplatin weekly instead of giving three weekly to reduce the toxicities and increase patients compliance to treatment . Many trials have showed that weekly cisplatin is a safe and less toxic than three weekly cisplatin. So weekly cisplatin is more acceptable and better alternative to three weekly cisplatin without compromise the efficacy.

A study conducted by Akihiro Homo et al on 53 locally advanced SCCHN patients by using weekly cisplatin 40 mg/m^2 with 70 Gy of radiotherapy in 35 fractions[47]. The overall survival rate and disease free survival was 93.7% and 88% respectively. All patients except one showed manageable toxicities.This study proved that weekly cisplatin is a better alternative with less toxicity without compromising the results.

The Basket University conducted a retrospective analysis on 53 SCCHN patients has shown that there was no significant difference in median overall survival in weekly and three weekly cisplatin arms. The loco regional control rate and distant relapse rate were similar in both arms . They have concluded that concurrent chemo radiotherapy with weekly cisplatin is as effective as three weekly cisplatin with very high bolus dose [48].

A study conducted by Tejpal Gupta et al at Tata Memorial Hospital, Mumbai on 264 cases with locally advanced SCCHN . All patients were given a 66 – 70 Gy radiotherapy with weekly cisplatin 30 mg/m^2. 65% of patients received planned cisplatin dose. The 5 year loco regional control was 46 %. The incidence of grade 3 mucositis was 29 %. The conclusion of the study was

weekly cisplatin has shown moderate efficacy with manageable toxicity. They have also concluded that weekly cisplatin is an optimal chemotherapeutic agent especially in a limited resource setting[49].

Tray nor et al, University of Wisconsin conducted a study about feasibility of weekly cisplatin with Intensity modulated Radiotherapy (IMRT) in locally advanced SCCHN. enrolled 57 patients were received weekly cisplatin dose of 30 mg/ m^2. The radiotherapy dose to gross tumor volume was 70 Gy. The study was conducted during a period of November 2001 to May 2007. The loco regional control and median overall survival was 85.5% and 86.9% respectively. The conclusion of the study was weekly cisplatin 30 mg/m2 along with IMRT with a GTV dose of 70 Gy is well tolerated [50].

In summary weekly cisplatin is well tolerated , less toxic and as effective as three weekly cisplatin for treating SCCHN patients concurrently along with radiation.

CISPLATIN

(cis-Diamminedichloroplatinum)

Classification:

Platinum compound, cytotoxic.

<u>Mechanism of action</u>:

It binds covalently to DNA and disrupts DNA function. It is similar to other the alkylating agents in action.

It binds covalently to DNA and inhibit the function of DNA. Once it entering into the cells, water molecules are replacing the chloride ligands. Because of this, positively charged platinum complexes are formed which in turns react with the nucleophilic sites of DNA. These complexes covalently binding to the DNA bases by use of intra-strand and inter-strand cross-links creating cisplatin-DNA adducts. This adducts will stop the synthesis of DNA, RNA and proteins. Cisplatin is cell cycle nonspecific agent. It also act as immunosuppressant, and radiosensitizers.

Metabolism

It is converted into several inactive metabolites non-enzymatically. These metabolites are highly bound to plasma proteins. Rapidly diffuses and highly concentrated into body tissues .Primarily excreted through the urine. Terminal half life of ultrafilterable platinum 20-45 minutes and for total platinum more than 5 days.

Table -2Adverse effects

Organ site	Side effects
Auditory function	ototoxicity (31%), abnormalaudiogram (24%), tinnitus (9%), vestibular toxicity rare.
Haematology	myelosuppression (25-30%) White Blood Cell nadir 18-23 days, platelet nadir 18-23 days , recovery 39 days ,anemia (25-30%)
Cardio vascular system	vascular toxicities like myocardial infarction, cerebrovascular accident,

	thrombotic microangiopathy or cerebral arteritis
Allergy	Hypersensitivity rarely occurs.
GIT	Highly emetogenic potential nausea and vomiting (> 90%) delayed nausea and vomiting.
Renal	Nephro toxicity
Neurology	Peripheral neuropathies
Liver	Increased LFT
Metabolic	Electrolytes disturbances

Dose

40 mg/m2 weekly along with concurrent radiation.

Dose modification is needed in myelosuppression and renal failure.

Administration Guidelines

Required dose of cisplatin injection is diluted in 500 ml of normal saline and infused at a rate of 40 drops per minute over 2 hours. This diluted cisplatin should be used within 24 hours. Any unused dilution should be discarded. Continuous infusion over 24 hours will reduce the nausea, vomiting and renal toxicity.

Recommended Clinical Monitoring:

Complete Haemogram , initially and then regular monitoring. Renal function tests including electrolytes , initially and then regular monitoring

Liver function tests- baseline and regular.

Clinical toxicity assessment for the following, neurotoxicity, ototoxicity and hypersensitivity, bleeding, infection, nausea and vomiting.

PREVIOUS ARTICLE RELEVENT TO PRESENT STUDY

A study on Palliative Hypofractionated Radiotherapy in Locally Advanced Head and Neck Cancer by Rajan Paliwal and team, Department of

Radiotherapy, Acharya tulsi Regional Cancer Treatment and Research Institute, Bikaner, Rajasthan University of Health Sciences, Jaipur, Rajasthan. India.

The aim of the above study was to assess the symptomatic relief, tumor response and acute toxicity of palliative radiotherapy in locally advanced HNC patients.

Methodology

50 previously untreated, histopathologically proven locally advanced SCCHN patients with hard fixed cervical node were included in the study. Patients with stage IV disease with hard fixed cervical nodes, ECOG performance status II and III with life expectancy of less than 1year were included.

All the Patients were treated by external beam radiotherapy by using Cobalt-60 teletherapy machine .A total dose of 20Gy was given in 4Gy per fraction , total of 5 fractions in 5 consecutive days of a week.

Patients characteristics:

Table -3

Patients details		No.of.patients
Sex	Male	40(80%)
	Female	10 (20%)
ECOG status	2	32 (64%)
	3	18 (36%)
main symtoms	Pain	48 (96%)
	Dysphagia	16 (32%)
	Hoarseness of voice	11 (22%)
	Respiratory distress	10 (20%)
	Other	3 (6%)
Primary site of the disease	Tonsil	12 (24%)
	Base of tongue	11 (22%)
	Hypo pharynx	14 (28%)
	Larynx	6 (12%)
	Other	7 (14%)
Tumor stage(T stage)	T3	27 (54%)
	T4	23 (46%)
Nodal stage (N)	N2	20 (40%)
	N3	30 (60%)

Response assessment

Response was assessed at 2 weeks and 4 weeks post treatment.

Table -4 Symptom relief (a)

Main symptom on presentation (No. of Patients)	Symptom Relief		
	No Relief (%)	Partial Relief (%)	Appreciable Relief (%)
Pain (48)	0(0.0%)	18(37.5%)	30(62.5%)
Dysphagia (16)	0(0.0%)	4(25.0%)	12(75.0%)
Hoarseness of voice (11)	1(9.1%)	2(18.20%)	8(72.7%)
Respiratory distress (10)	1(10.0%)	2(20.0%)	7(70.0%)

Appreciable relief means ≥ 50% symptomatic relief
Partial relief means < 50% symptomatic relief

Table – 5 Overall response (a)

Response	Number of patients	
	15th day	30th day
CR	2 (4%)	4 (8%)
PR	26 (52%)	46(92%)
SD	22 (44%)	0

Table – 6 Acute toxicity

Time of follow-up	Acute skin reaction				Acute mucosal reaction			
	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV
15th day	10 (20%)	0	0	0	7 (14%)	0	0	0
30th day	31 (62%)	19 (38%)	0	0	27 (54%)	21 (42%)	2 (4%)	0

Conclusion

In that study, they observed that two third of the patients presented with multiple symptoms and the short course of palliative radiotherapy provided appreciable symptom relief to more than 50% of the patients. At one month post palliative radiotherapy 92% of the patients showed partial response. Further radiotherapy was given according to the tumor regression status.

It was concluded that unfavourable advanced and unresectable HNC can be identified for a suitable short course palliative radiotherapy which will achieve growth restraint and durable symptom relief in sizeable proportions of the patients.

AIM OF THE

STUDY

AIM OF THE STUDY

AIMS AND OBJECTIVES:

PRIMARY OBJECTIVES

To assess for degree of symptomatic relief & palliation.

To assess the proportion of patients eligible for radical chemo radiotherapy.

To assess immediate loco-regional disease control.

SECONDARY OBJECTIVE

To assess the acute toxicity to the treatment.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is single arm prospective study involving 30 unresectable and advanced squamous cell carcinoma head and neck cancer patients. Thirty patients with histologically proved squamous cell carcinomas registered in our department were enrolled in this study. Enrolment of the patients was started after obtaining consent from the ethical committee for conducting this study in our institute. The informed consent was obtained from all the patients before including in the study.

All patients were given short course palliative radiotherapy of 20 Gy.(400cGy per fraction for five fractions totally). Response was assessed after 1 month of radiotherapy. Patients achieving symptom relief of more than 50%,

partial response at primary/nodal sites with good general condition were given further chemo radiotherapy at curative intent. For other patients best supportive care was given.

INCLUSION CRITERIA:

- Biopsy proven squamous cell carcinoma of the head & neck (SCCHN)
- Primary tumour sites: oral cavity, oropharynx, hypopharynx, larynx

- Stage 4B disease
- Stage 4A and Stage 3 disease with poor Performance status (PS)
- ECOG performance status 2 and 3
- Age < 70 years
- Signed informed consent prior to initiation of protocol specific procedures

EXCLUSION CRITERIA:

- ECOG/PS 4
- Inadequate hepatic, renal functions and bone marrow reserve.
- Previously received Radiotherapy or/and chemotherapy for any other malignancy
- Tumours of nasal cavity, paranasal sinuses, nasopharynx and salivary glands
- Non squamous histopathology and Metastatic disease.
- Uncontrolled medical co-morbidities

INVESTIGATION DETAILS (PRE TREATMENT WORK UP)

Detailed history.

Complete physical examination.

Biopsy from the primary or metastatic node.

Blood grouping.

Clinical history/assessment.

Complete haemogram.

Renal function test(RFT)

Liver function test(LFT)

Fine needle aspiration cytology from doubtful lymph node

Chest x-ray.

ENT examination.

Contrast enhanced computed tomography scan (CECT) of face and neck - At base line and after 1month of treatment.

Base line symptom assessment by using symptom assessment scale (SAS).

PRE TREATMENT PATIENT PREPERATION

Dental care:

Dental prophylaxis was done in all required patients. It includes dental filling, scaling and extraction. In case of extraction of teeth, all patients were started on antibiotics, 2-3 days before to the extraction and then maintained on antibiotic coverage for 7 to 10 days. In already edentulous patient surgical removal of any symptomatic cysts and infected retained root tips were done. Complete oral hygiene instruction was given. Following dental extraction rest time of 2 weeks was given for proper wound healing.

Oral care:

Most important therapy related toxicity in head and neck cancer treatment is Mucositis .

Patients were asked to gargle four to six times a day by using soda bicarb dissolved in water especially after food during radiation. Patients developing oral candidiasis were treated with tablet Fluconazole 100 mg po for 7 to 10 days.

Nutritional support:

Most of HNC patients lose weight due to cancer and treatment related toxicities. So nutrition management is very important to prevent/ reduce the treatment related complication like weight loss. Nutritionmanagement includes multidisciplinary team consists of dietitian, speech-language/swallowing therapist.

Head and neck patients have a specific feeding problems. All the patients were encouraged to take adequate nutrition to prevent excessive weight loss. Nasogastric tube is inserted if required. In extreme cases where nutritional intake by conventional methods is not possible as a result of concurrent chemo radiation, parenteral nutrition is given.

Specific meal plans were devised for individual patients. The meal plans were maintained as close to the normal diet as possible even when the texture and consistency were changed. The patient's weight was checked weekly to evaluate the patients nutritional status. Depending on the weight the meal plans are revised once in a week. The meal plans are made keeping in mind of the increased caloric and protein requirements of the patient for tissue regeneration.

From the third week of treatment onwards the patients were advised to take liquid based diet as radiation induced reactions were started by that time.

Since the patients had radiation induced dysphagia and mucositis, the specific meal plan was changed to incorporate mainly liquid diet. During the fourth week of radiation patients had developed xerostomia, so there was difficulty in swallowing solid foods. Mucosal dryness will cause the solid foods to stick to mucosa and induces vomiting. The patients were advised to take fresh juices like apple and guava and avoid citrus fruits like lemon and Mozambique. A special home- made high protein food using banana, egg, milk and sugar were advised twice daily.

Nasogastric tube insertion or feeding jejunostomy and parenteral feeding was given to patients for whom oral feeding was not feasible.

Smoking cessation:

Hypoxia due to high levels of carboxyhemoglobin in tobacco smokers coassociated with the poor treatment outcome. Hence strong motivational support is given to all patient to quit smoking before starting the study.

PRE TREATMENT ASSESSMENT OF SYMPTOMS

Before starting the treatment patients symptom was assessed by using symptom assessment scale (SAS).

Symptom assessment scale

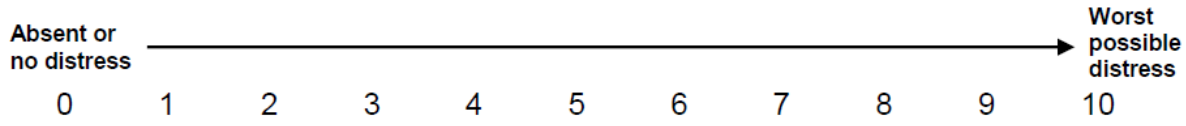
The Symptom Assessment Scale (SAS) describes the patient's level of distress relating to individual physical symptoms. The instrument was designed to be a patient rated tool.

How to assess?

Patient can rate the degree of their distress for each symptom. If patient is not able to do so, family members/ attenders are asked to rate the degree of distress. But it is better for the patient to rate the symptoms on their own using the Symptom Assessment Scale for accuracy and consistency.

Figure- 5; 11 point numeric scale

11 point numeric scale was used to assess the symptom.



If there is no Symptom, rating was given as '0'. If Symptoms present rating was given from 1 to 10.

All the patients were told that, A score of 0: no symptoms

A score of 1:minimal distress

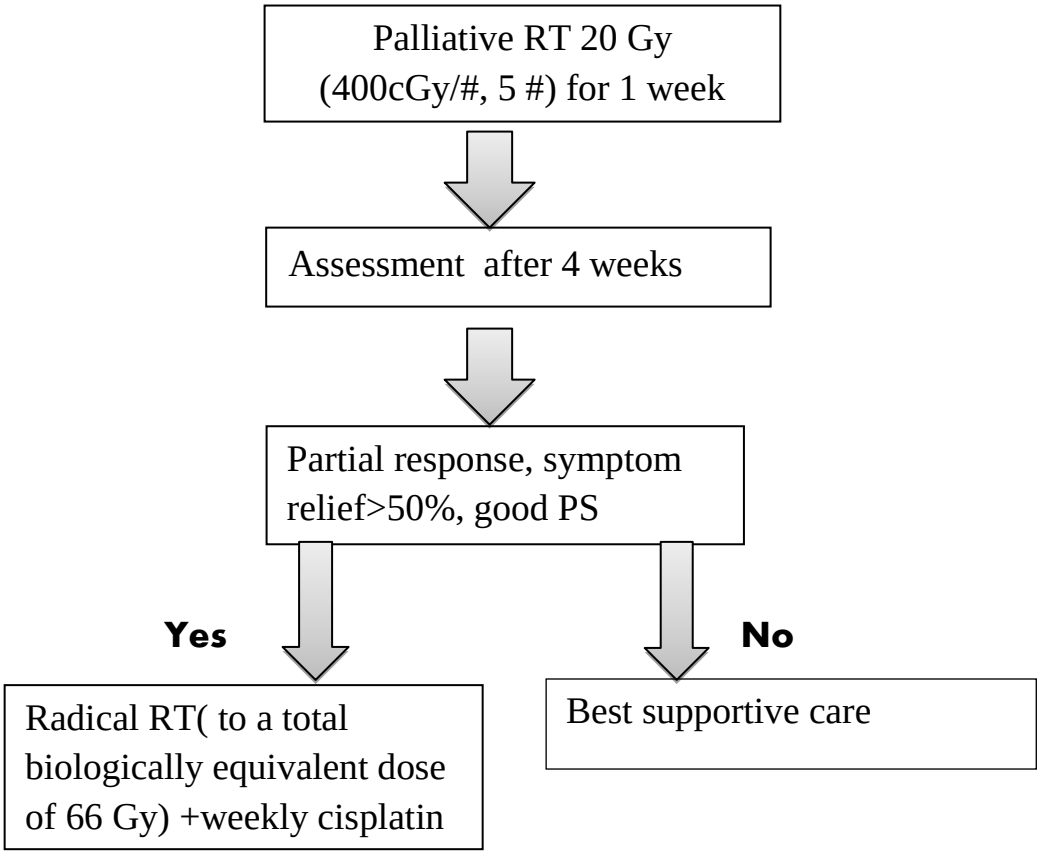
A score of 10: the worst possible distress.

Pain, dysphagia, dysnea, otalgia, cough and insomnia are the main distressing symptoms that were assessed.

Assessment was done at baseline then every week after starting the treatment and at 1 month post treatment.

PROTOCOL DESIGN

A total of 30advanced and unresectable SCCHN patients attending Radiotherapy OP were recruited to the study.



All patients were treated with 20Gy of radiotherapy in 5fractions of 400cGy each. Response was assessed after 1 month of radiotherapy. Patients achieving symptom relief of more than 50%, partial response at primary/nodal sites with good general condition were given further chemo radiotherapy at curative intent.

Best Supportive Care(BSC) was given for other patients who were not showing partial response and symptom relief of less than 50% with poor general condition at 1 month post treatment.

RADIOTHERAPY TECHNIQUE

Patients were treated by external beam radiotherapy delivered by Cobalt-60 teletherapy machine (Theratron phoenix).

POSITION

Patients were treated in right and left lateral positions.

PORTALS

Patients with disease crossing the midline and had bilateral presentation were treated by bilateral Parallel opposed fields and dose was being prescribed to midline.

TREATMENT VOLUME

Treatment volume included primary tumor site and involved neck region plus 1 cm margin for setup error.

DOSE OF PRT (palliative radiotherapy)

A total dose of 20Gy is given in 5 fractions in 5 consecutive days with a dose of 4Gy per fraction from day 1to day 5(from Monday to Friday). Surface bolus was used for fungating lymph nodes.

RESPONSE ASSESSMENT

These patients were evaluated after 4 weeks of palliative radiotherapy and assessed for treatment response in terms of disease control(tumor regression) using RECIST criteria and degree of palliation of symptoms using Symptoma Assessment Scale(SAS). Acute toxicity grading was done as per RTOG (Radiation Therapy Oncology Group) toxicity criteria. Further treatment(chemo radiotherapy) was given according to the tumor regression status.

RESPONSE EVALUATION: at 4th week of palliative radiotherapy

SUBJECTIVE RESPONSE

Degree of symptomatic relief and palliation by using symptom assessment scale

Toxicity assessment—common toxicity criteria. (NCI CTCAE v 3.0)

OBJECTIVE RESPONSE

Objective response of primary and nodal tumor was assessed by clinically and radiologically by using response evaluation criteria in solid tumors (RECIST)

COMPLETE RESPONSE(CR):

Absence of residual disease after treatment

PARTIAL RESPONSE (PR):

30% decrease from baseline at 4^{th} week

STABLE DISEASE (SD):

Neither sufficient shrinkage nor sufficient increase in size.

PROGRESSIVE DISEASE(PD):

20% increase from base line.

FURTHER CHEMO RADIOTHERAPY

Further Radiotherapy was delivered at 200cGy/# to achieve a total biological equivalent dose (BED) 66 Gy with same radiation portals that were used in palliative radiotherapy(PRT). Further radiotherapy dose was calculated

by the time-dose-fraction (TDF) method taking into account the dose fraction schedule of palliative radiotherapy (PRT) and the subquent gap in days.Spinal cord shielding was done at 40 Gy to avoid the dose to spinal cord.This further radiotherapy was given along with weekly chemotherapy of inj. Cisplatin 40 mg/m^2.

CHEMOTHERAPY

All blood parameters like complete blood count (CBC)and the basic metabolic parameters were assessed before the start of every cycle of chemotherapy. Inj.cisplatin $40mg/m^2$ was given concurrently with further curative intent radiotherapy.

PREMEDICATION

All patients were given the following premedication half an hour before starting thechemotherapy.

1. Inj. Dexamethasone 8 mg iv
2. Inj. Rantac 150 mg iv
3. Inj. Avil 1 4mgiv
4. Inj. Ondanseteron 8 mg iv

After premedication, patients were given prehydration with 500 ml of normal saline. Cisplatin was given in 500 ml normal saline infusion at a rate of 40 drops per minute.Inj. Mannitol 175 ml IVgiven immediately after inj.cisplatin. After mannitol injection, hydration was again done by using 500 ml of normal saline. The entire chemotherapy procedure was completed within 4 hours. The radiation therapy was given within one hour of completion of chemotherapy. The patients were given inj. Ondanseteron 8 mg IV bd daily for three weeks.

ASSESSMENT IN BETWEEN TREATMENT

Toxicity of radiotherapy the following toxicities were assessed during every week of radiation.

Skin reactions

Mucositis

Dysphagia

Xerostomia

Laryngitis

Toxicity ofchemotherapy (Cisplatin)

the following toxicities were assessed during every week of treatment.

Nausea

Vomiting

Renal function alteration

Peripheral neuropathy

TOXICITY MANAGEMENT

The nausea and vomiting were managed by antiemetics, ondanseteron 8 mg iv twice daily. The patients were also given adequate i v fluids to prevent dehydration. If any alteration in the renal parameters noted, nephrology opinion was sought and the dose of cisplatin was modified accordingly.

The toxicities were assessed using RTOG Acute Morbidity Scoring Criteria and Common Toxicity Scoring Criteria. The toxicities were assessed every Monday and recorded. All the toxicities were managed according to the guidelines.

For prevention of mucositis all patients were advised to maintain good oral hygiene and Soda bicarb mouth wash gargling 5 -6 times a day. Patients were also instructed to apply honey 15 minutes prior to the radiation, 15

minutes after radiation and 12 hours after radiation. During the radiotherapy, if patients developed mucositis, they were treated by using analgesics(NSAIDS), low dose steroids and antibiotics. NSAIDS used was Diclofenac sodium tablets 50 mg twice daily. The steroid used was dexamethasone 4 mg IV twice daily if the patients developed grade III mucosities. All patients with grade III mucositis were treated with antibiotic, Cephalexin 500 mg four times daily. NSAIDS and antitussives was given forof grade II pharyngitis and laryngitis .Steroids were included in the management of all grade III toxicities.

Hemoglobin was checked every week. If hemoglobin level went below 10 mg%, the patients were given packed cell transfusion.

TABLE - 7: RTOG Acute Morbidity Scoring Criteria

Grade	0	1	2	3	4
MUCOSITIS	No Change	Injection / Mild pain not requiring analgesic	Patchy mucositis Moderate pain needs analgesia	Confluent Mucositis Severe pain, needs morphine	Ulceration, hemorrhage and Necrosis
DERMATITIS	No Change	Follicular, faint, dull erythema/ epilation/ desquamation	Tender, bright patchy moist desquamation	Confluent moist desquamation	Ulceration, hemorrhage and Necrosis
SALIVARY GLAND	No Change	Mild dryness / Altered taste	Moderate to complete dryness	---------	Necrosis

PHARYNX	No Change	Mild dysphagia requiring analgesics	Moderate dysphagia requires narcotics. Liquid diet	Requires IV fluids or NG tube	Ulceration, perforation and fistula
LARYNX	No Change	Mild Hoarseness, Cough doesn't need treatment	Persistent hoarseness, Cough requiring antitussive	Whispered speech, throat pain requiring narcotics	Dyspnea/ stridor, hemoptysis with tracheostomy
WBC (X1000)	>= 4.0	3 – 4	2 – 3	1 – 2	<1
PLATELET (X1000)	>=100	75 – 100	50 – 75	25 – 50	< 25 or spontaneous bleeding
HEMOGLOBIN **(gm %)**	>11	9.5 – 11	7.5 – 9.5	5.0 – 7.5	-------

FOLLOW UP OF PATIENTS RECEIVING FURTHER CHEMO RADIOTHERAPY

Patients received further chemo radiotherapy with curative intent were assessed for disease status 6 weeks after the treatment subjectively and objectively(by computed tomography). Patients were followed up every month thereafter.

BEST SUPPORTIVE CARE FOR PATIENTS NOT GOING FOR FURTHER CHEMO RADIOTHERAPY

Poor responders (symptom relief of less than 50% and patients not showed partial response)with poor general condition at assessment after1 month of palliative radiotherapy of 20 Gy, were not taken up for further chemo radiotherapy. Best supportive care(BSC) was given to these patients.

Supportive care was given in respect to the following aspects.

Management of cancer pain, vomiting , cancer and treatment related anemia, fatigue due to cancer and distress management.

Prevention and treatment of infections due to cancer .

Palliative care and nutrition support.

Pain management

All patients were registered in palliative care OP department. After assessing the patients properly, T.morphine 5mg fourth hourly/ six times a day was given along with anti depressants, sedatives and laxatives. All the patients were reviewed once in a week.

Packed cell transfusion was given to the required patients. Proper cleaning and dressing was done for ulcerated, fungated nodes and skin involving primaries. Patients were kept on higher antibiotics coverage for 7 to 10 days.

Nutrition support

Adequate nutrion support was given to all patients. Naso Gastric tube insertion and feeding was done for patients not taking orally. All patients were advised to fresh juices like apple and guava. A special home- made high protein food using banana, egg, milk and sugar were advised twice daily. Protien powder contains high calorie rich in protiens was given to all patients. for extreme cases, parenteral nutrion was given. All the patients were reviewed once in a week.

CASE ANALYSIS

AND RESULTS

RESULTS

AGE DISTRIBUTION

Totally 30 patients were enrolled in the study. Eligible age limit for the study was from 18 to 70 years of age.

Table - 8

AGE GROUP (in Years)	NO.OF.PATIENTS	PERCENTAGE(%)
30 – 40	3	10
40 – 50	5	16.6
50 – 60	12	40
60 – 70	10	33.3

The age of the patients ranged from 34 to 68 years. The median age of the patients included in the study was 56 years. Age distribution analysis of the sample showed that, most of the patients were in age the group of above 50 years. Age of the youngest patient included in the study was of 34 years; age of the eldest patient was of 68 years old.

SEX DISTRIBUTION

The study group consists of 24 males and 6 females.

This skewed selection towards the male gender was probably due to the increased exposure of carcinogens in male than females.

Table-9; sex distribution

SEX	NO.OF.PATIENTS (%)
MALE	24(80%)
FEMALE	6 (20%)

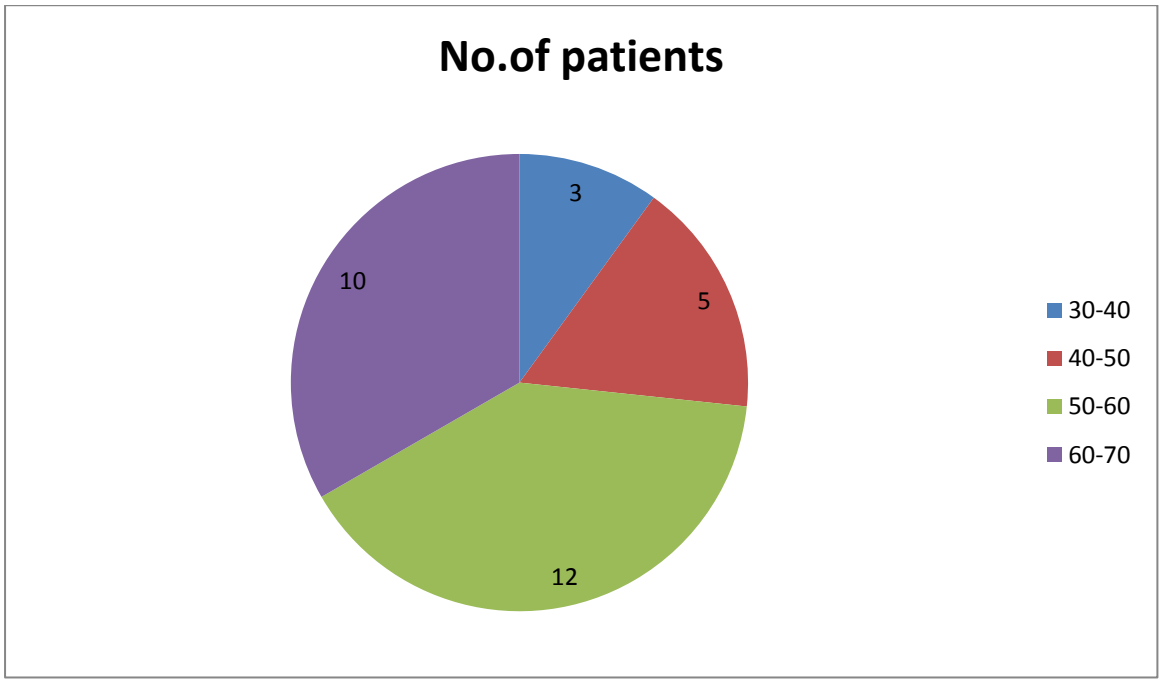
ECOG PERFORMANCE STATUS

Table -10

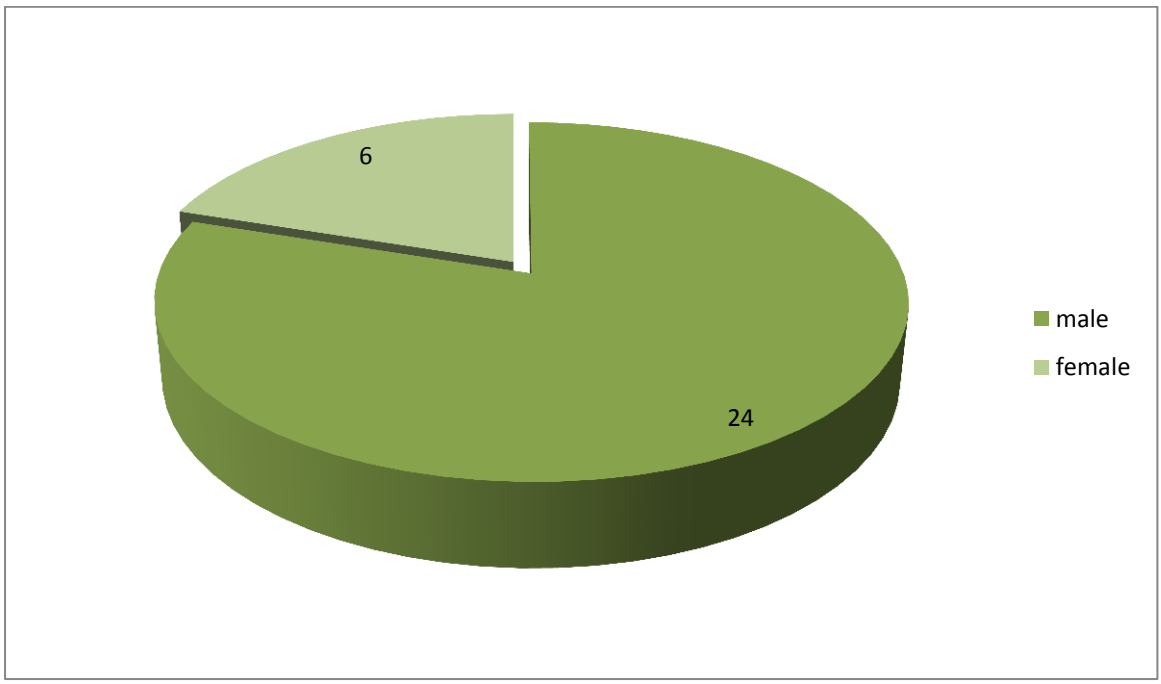
ECOG STATUS	NO.OF.PATIENTS (%)
ECOG 2	22(73.3%)
ECOG 3	8(26.7%)

Patients with poor performance status (ECOG 2 and 3) and high disease burden Were included in the study.

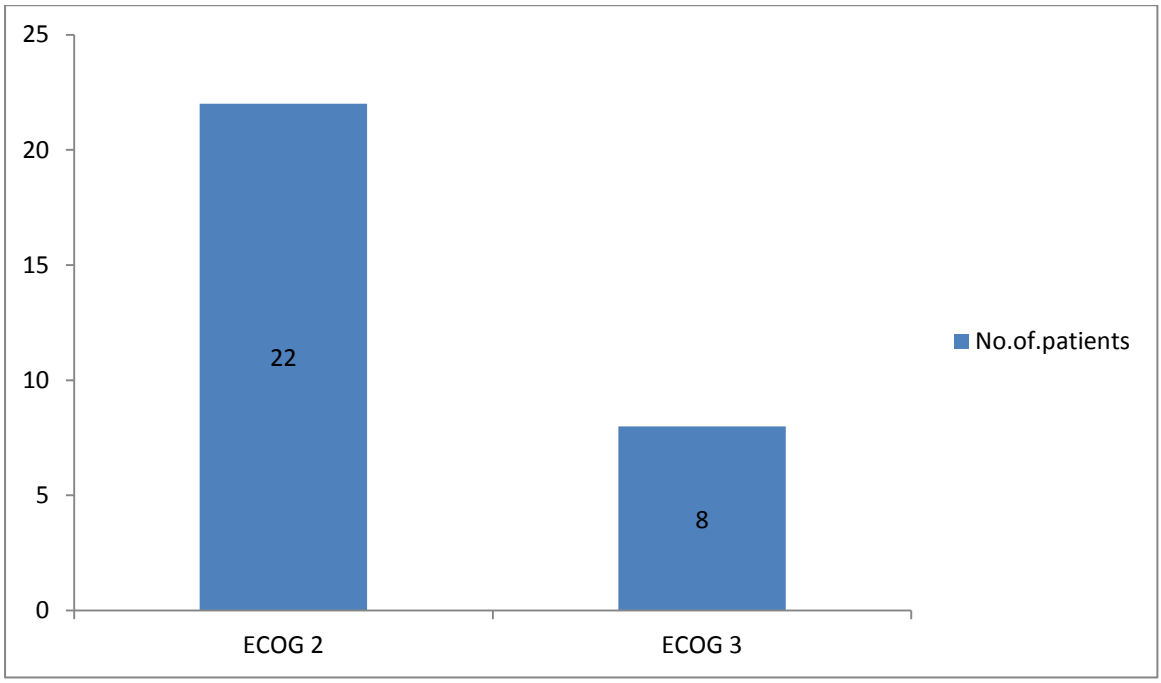
AGE DISTRIBUTION



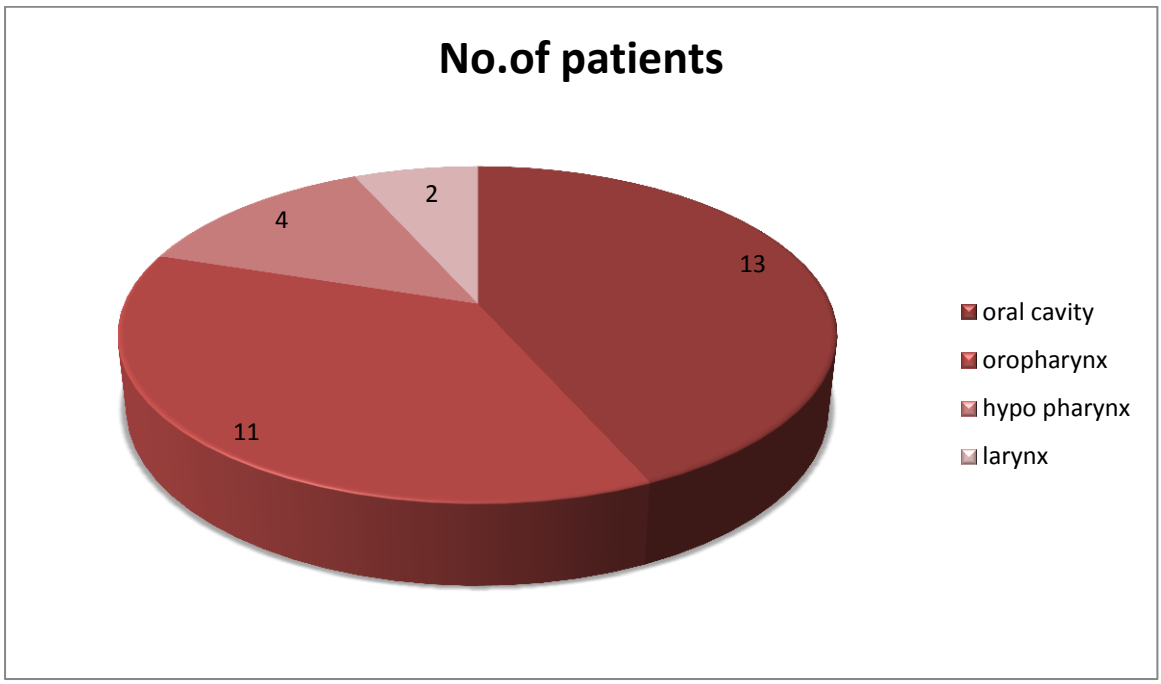
SEX DISTRIBUTION (no. of patients)



ECOG STATUS



SITE DISTRIBUTION



SITE DISTRIBUTION:

The site wise distribution of the cancers patients included in the study showed, majority of the patients were of oral cavity and oropharyngeal carinoma.

Table -11

Site	No.of.patients	Percentage(%)
Oral cavity	13	43.3
Oropharynx	11	36.7
Hypopharynx	4	13.3
Larynx	2	6.7

SUBSITE INVOLVEMENT:

ORAL CAVITY -SUB SITE DISTRIBUTION

The patients with oral cavity cancers had involvement of the anterior 2/3rd of the tongue in 5 patients; buccal mucosa in 3 patients; alveolar ridge in 3 patients; floor of mouth in 1 patient and hard palate in 1 patient.

Table-12

Sub site	No.of.patients
Anterior 2/3 rd tongue	5
Buccal mucosa	3
Alveolar ridge	3
Floor of mouth	1
Hard palate	1

HYPO PHARYNX-SUB SITE DISTRIBUTION

Table- 13

Sub site	No.of.patients
Pyriform fossa	3
Post cricoids	1

In hypo pharyngeal cancers patients, 3 of them pyriform fossa involvement and 1 post cricoid region involvement.

LARYNX- SUB SITE DISTRIBUTION

Two supraglottic cancer patients were included in the study.

OROPHARYNX- SUBSITE DISTRIBUTION

Table-14

Sub site	No.of.patients
Posterior 1/3rd tongue	5
Tonsillar fossa	4
Soft palate	2

In cancer of the oropharynx patients, involvement of the posterior one third tongue in 5 patients; tonsillar fossa in 4 patients and the soft palate in 2 patients.

PRIMARY TUMOR CHARECTERISTICS

Table -15; T STAGE

T stage	No.of.patients
T2	5
T3	9
T4a	11
T4b	5

Majority of the patients were in T4 stage.

5 patients in T2 stage;

9 patients were in T3 stage;

11patients were in T4a stage and 5 patients were in T4b stage.

Table -16; N stage distribution

N stage	No.of.patients
N0	2
N1	4
N2a	7
N2b	6
N2c	6
N3	5

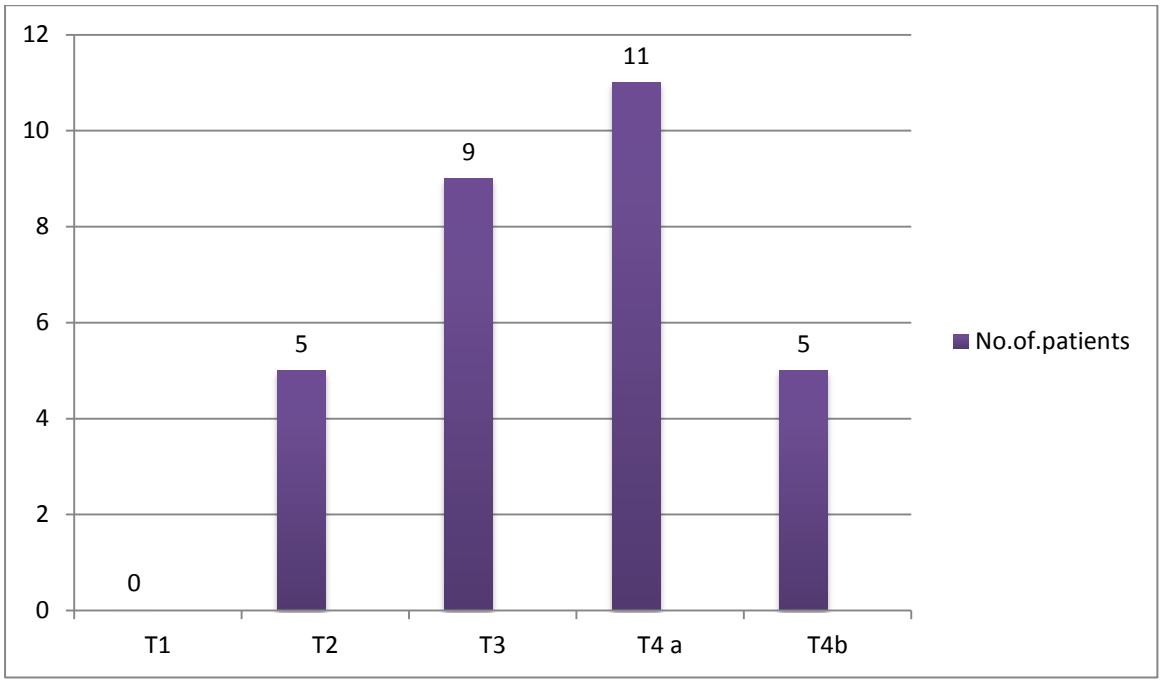
Majority of the patients were N2 stage 19.

5 of the patients were in N3 stage. Out of them 4 patients were presented with ulcerated, fungating nodes.

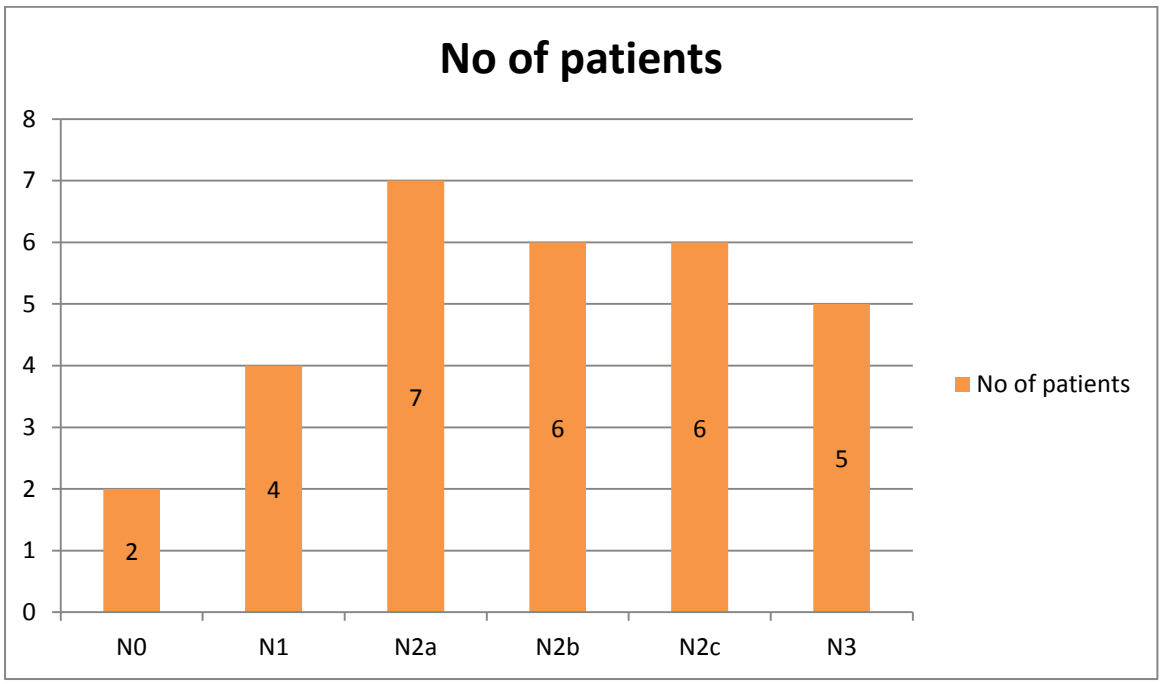
N0 nodal staging was found in 2 patients.

N1 presentation was in 4 patients.

T STAGE



N STAGE



STAGE GROUPING

Table –17

Stage group	No.of.patients
Stage III	8
Stage IVA	15
Stage IV B	7

Most of the patients were in stage group IV A.

DIFFERENTIATION

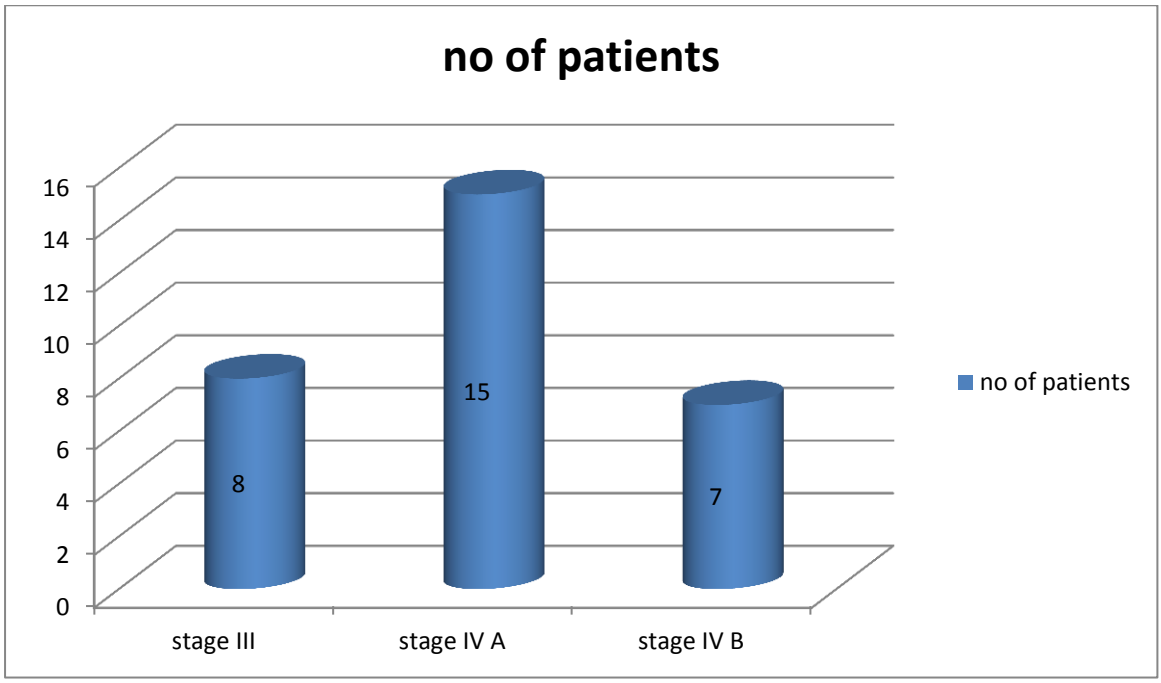
Table -18

Differentiation	No.of.patients
Well differentiated	3
Moderately differentiated	5
Poorly differentiated	22

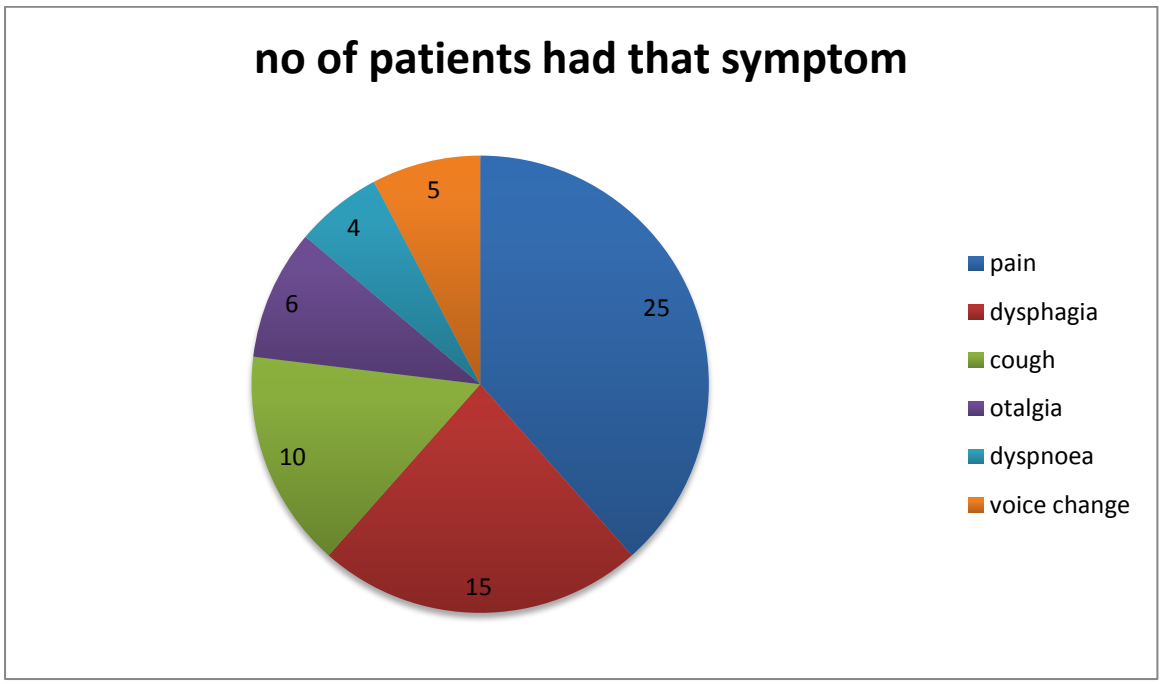
Poorly differentiated carcinomas accounts for 73.33%.

Moderately differentiated cancers in 16.6%. Well differentiation was seen in 10%.

STAGE GROUPING



SYMPTOM AT PRESENTATION



SYMPTOMS BEFORE PRT (Palliative Radiotherapy)

Table -19; Symptoms at presentation

Symptoms	No.of.cases had that symptom
Pain	25 (83%)
Dysphagia	15 (50%)
Cough	10 (33%)
Otalgia	6 (20%)
Dyspnoea	4 (13%)
Voice change	5 (16%)
Insomnia	23 (76%)

Pain was the major compliant in 83% of the patients.

Dysphagia, cough, otalgia, insomnia, dysnea and voice change was seen in 50%, 33%, 20%,76%,13% and 16% of the patients respectively.

Some of the patients had all the above said symptoms, while others had half or more than half of the above mentioned symptoms.

RESPONSE ASSESSMENT FOLLOWING PALLIATIVE RADIOTHERAPY

Table -20 Over all response (b) (n=30)

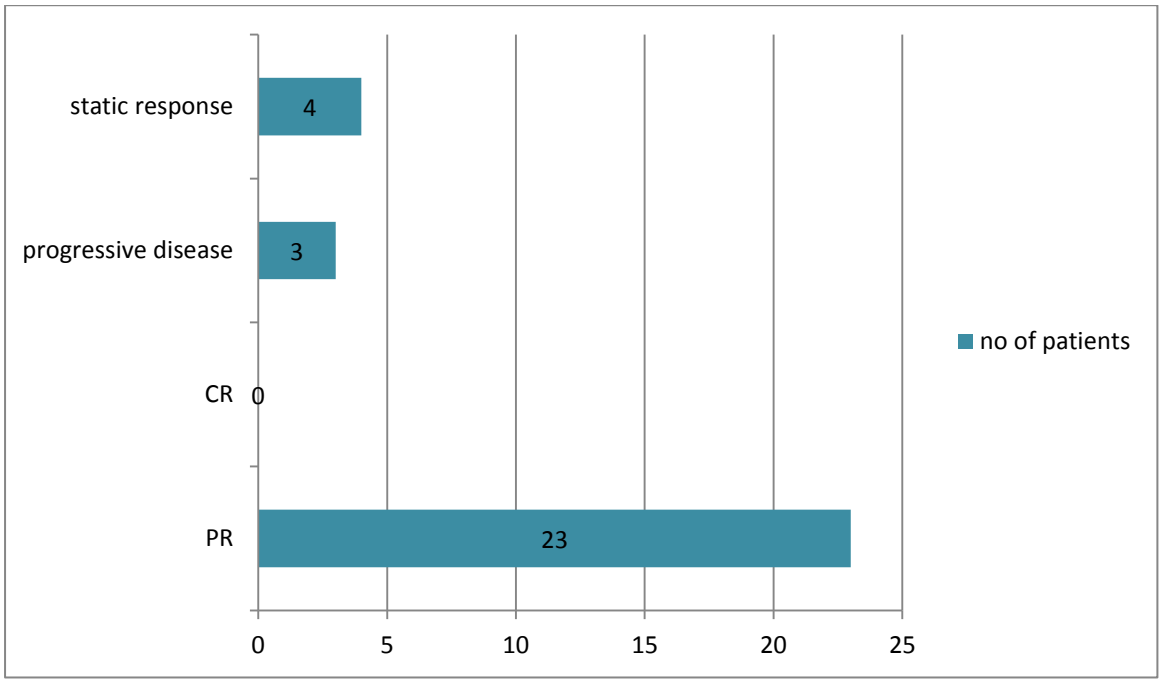
Type of response	No.of.patients
Partial response	23 (76.6%)
Static response	4 (13.4%)
Progressive disease	3(10%)
Complete response	0(0%)

SYMPTOM RELIEF

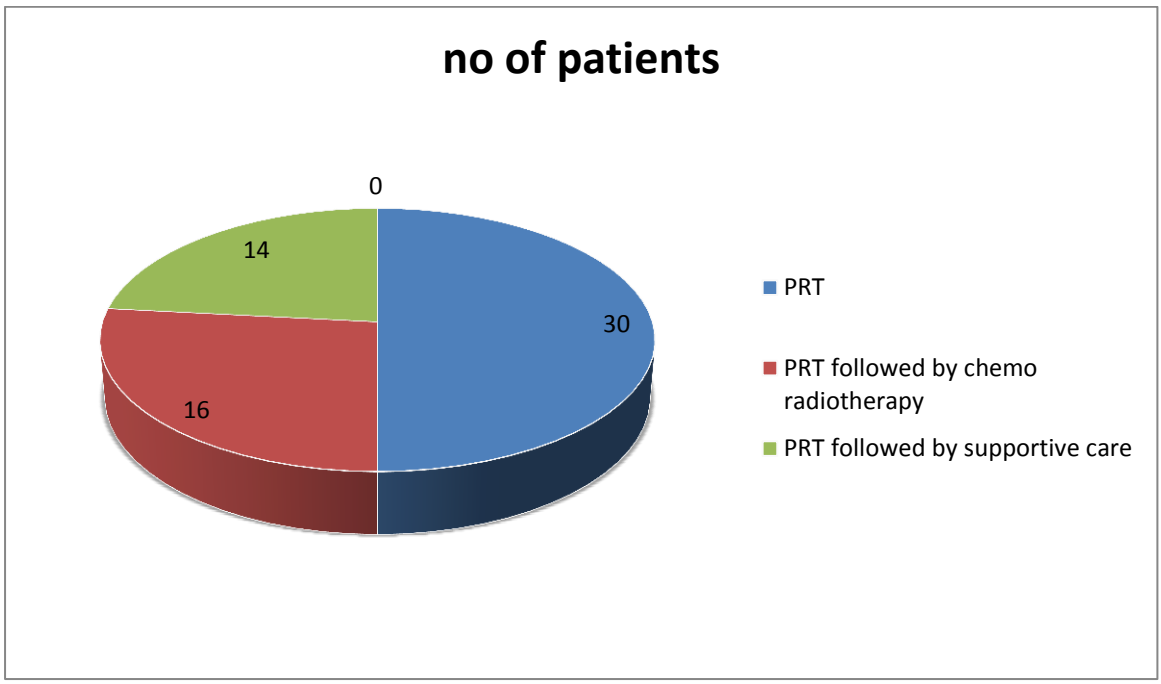
Table -21 Symptom relief (b)

Symptoms	No.of patients showed more than 50% symptom relief
Pain **(n=25)**	20 (80%)
Dysphagia **(n=15)**	11 (73%)
Cough **(n=10**)	7 (70%)
Otalgia **(n=6)**	4 (66%)
Dyspnoea **(n=4)**	3(75%)

RESPONSE AFTER PALLIATIVE RADIOTHERAPY



PATIENTS ELIGIBLE FOR FURTHER CHEMO RADIOTHERAPY



Voice change **(n=5)**	2 (40%)
Insomnia **(n=23)**	18 (78%)

PROPORTION OF PATIENTS ELIGIBLE FOR FURTHER CHEMO RADIOTHERAPY WITH CURATIVE INTENT

Out of 30 patients who received palliative radiotherapy, 16 patients were eligible for further chemo radiotherapy with curative intent. Remaining 14 patients were not fit for further treatment, so Best Supportive Care was given to them.

Table – 22 Further chemo radiotherapy (n=30)

Radiotherapy received	**No.of.patients**
Palliative radiotherapy	30
Palliative RT followed by Further chemo radiotherapy with curative intent.	16 (53%)
Palliative radiotherapy followed bysupportive care.	14 (47%)

RESPONSE ASSESSMENT FOLLOWING CHEMO RADIOTHERAPY

1 month after the completion of the concurrent chemo radiation(with curative intent), the response rates were assessed.

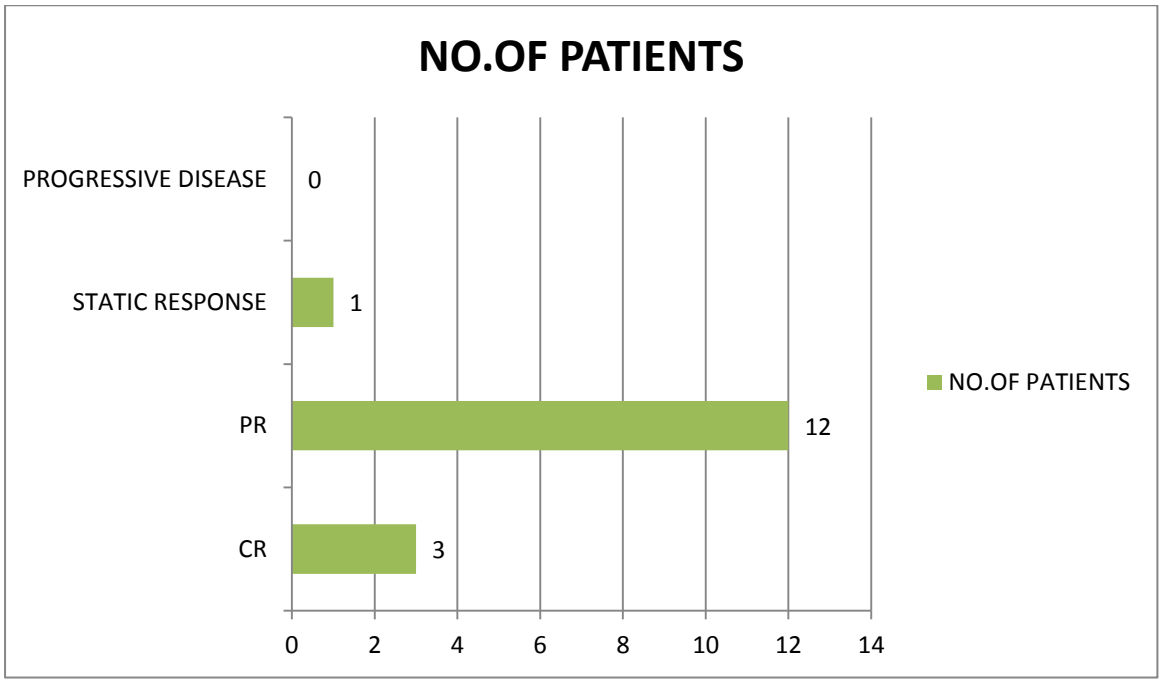
Table – 23 Over all response (c) (n=16)

Response	No.of.patients
Complete response	3 (18.75%)
Partial response (**presented with minimal residual disease**)	12 (75%)
Static response	1 (6.25%)
Progressive disease	0 (0%)

Clinically complete response was seen in 3 (18.75%) cases. Static response was noted in 1 (6.25%) patients. No one has developed progressive disease.

Locoregional control was very good in remaining 12(75%) patients. They were presented with very minimal residual disease at 1 month post treatment.

RESPONSE AFTER CHEMO RADIOTHERAPY (n=16)



ANALYSIS OF THERESPONSE

Clinically, complete response was achieved in 3 patients. All the 3 patients were poorly differentiated carcinoma of posterior one third of tongue.

All the patients were belong to stage group IV A. Staging was T4A N2b M0 in one patient and T4a N1 M0 in two patients.

Both the patients were in ECOG status 2.

TOXICITY ASSESSMENT

TOXICITY OF PALLIATIVE RADIOTHERAPY:

Total dose of 20 Gy was delivered in 4 Gy per fractions, total of 5 fractions over 5 days a week. The toxicities of palliative radiotherapy were graded using RTOG acute morbidity scoring criteria.

Mucositis:

Majority of the patients developed grade 1 mucositis only. (20 patients).

Grade 2 mucositis was noted in 10 patients.

No patients were developed grade 3 or more toxicities due to treatment.

The mucositis was managed with,

1. Inj. Dexamethasone 8 mg IV BD
2. Soda Bicarbonate Mouth Wash every 3-4 hours.
3. Alcohol free Antibacterial Mouthwash / oral lozenges.
4. Dispersible pain killer tablets to relieve pain.

Dermatitis:

This was not a significant problem in this study. Most of them had grade 1 reaction only.

No other toxicity was developed due to palliative radiotherapy.

TOXICITY OF FURTHER CHEMO RADIOTHERAPY:

Further chemo radiotherapy was delivered to patients who showed partial response, symptom relief of more than 50% with good general condition. It was given in 2 Gy per fractions upto a total dose of 66Gy radio biological equivalent with weekly Inj.Cisplatin 40 mg/m^2 .

The toxicities occurred during radiotherapy were graded using RTOG acute morbidity scoring criteria.

Mucositis:

Majority of the patients developed grade 2 mucositis (11 patients). 2 patients developed grade 3 mucositis and treatment had to be suspended to allow for the resolution of mucositis before proceeding with further radiation.

Dysphagia:

After palliative radiotherapy dysphagia was appreciably relieved in majority of the patients. Out of 16 patients who received further radiotherapy, 8 patients showed increased dysphagia (from grade 1 to grade 2). They were managed with pain killer and maintained on nutritious liquid diet. No patients developed grade 3 or more reactions.

Dermatitis:

Most of them developed grade 1 and grade 2 reactions which was allowed to resolve by itself after the completion of treatment.

TOXICITY OF PALLIATIVE RADIOTHERAPY

Mucositis (n=30)

Mucositis	No. of. patients
Grade 1	20
Grade 2	10
Grade 3	0
Grade 4	0

TOXICITY OF FURTHER CHEMO RADIOTHERAPY

Mucositis (n=16)

Mucositis	No.of. patients
Grade 1	3
Grade 2	11
Grade 3	2
Grade 4	0

Dysphagia (n=16)

Grade	No.of.patients
Grade 1	7
Grade 2	9
Grade 3	0
Grade 4	0

Dermatitis

Grade	No. of. patients
Grade 1	10
Grade 2	6
Grade 3	0
Grade 4	0

Salivary gland toxicity:

Almost all of the patients who received further radiotherapy, have developed grade 2 toxicity at the first assessment . But none had acute necrosis of the salivary gland. All of those who had xerostomia were prescribed artificial salivary supplements.

Haematological toxicity

The only haematological toxicity encountered during the study was anaemia. None of the patients had neutropenia or thrombocytopenia.

Table-24 Anaemia

Grade	No.of. cases
Grade 1	10
Grade 2	4
Grade 3	0

TOXICITY OF WEEKLY CDDP:

All the 16 patients received weekly Cisplatin of 40 mg/m^2during radiotherapy. They received 4 cycles of chemotherapy. Nausea and vomiting was observed in most of the patients.

NAUSEA

Table -25

Grade	No.of cases
Grade 1	7
Grade 2	9
Grade 3	0

Table – 26 VOMITTING

Grade	No.of cases
Grade 1	9
Grade 2	2
Grade 3	0
Grade 4	0

Nausea and vomiting was managed with,

IV fluids to correct dehydration, if any.

Metoclopramide 40 mg PO every 4–6 hours for 4 days.

Dexamethasone 4-8 mg IV BD for 4 days.

DISCUSSION

DISCUSSION

M ajority of these cases (60%-80%)in India are presented in advanced stage. Management of these cases with curative approach has evolved considerably over the time. There was lot of randomized control trials, meta analyses and volume of literatures on this already. Radical treatment in the form of aggressive multi modality approach is not successful in all of these patients because of poor performance status and unresectability. These advanced and unresectable cases need palliative treatment and/or best supportive care.

There is no general consensus Regarding palliative schedule in SCCHN. Many palliative regimens are recommended. Weissberg et al[51] evaluated conventional fractionated radiotherapy versus hypofractionated palliative radio therapy schedules for patients with locally recurrent or advanced HNC. They compared 60 Gy to 70Gy over 6 to 7 weeks with 40 Gy to 48 Gy in 64patients with stages III and IV surgically unresectable SCCHN. No difference was observed in terms of tumor control, acute toxicity and chronic toxicity.

Sushmita Ghoshal et[52] al (2004) conducted another study to assess the role of palliative radiotherapy for symptom control in patients with locally advanced SCCHN. In that study, 25 cases with stage 3 and 4 HNC were treated with a short course of palliative radiotherapy of 30 Gy, 3 Gy per fraction, in 10 # over two weeks. Baseline symptoms were assessed using an 11 point numerical scale for pain, dysphagia, cough, insomnia and dyspnea. The primary end point of the study was relief of symptoms at 4th week after radiotherapy. All 22 patients with pain and 90% of patients with dysphagia, dyspnea and disturbed sleep had greater than 50% relief in symptoms after radiotherapy. Cough was relieved in 60% of cases.

In another study conducted by Rajan paliwal et[42] al, palliative radiotherapy dose of 20Gy was delivered in 5# in 5 consecutive days with a dose of 4Gyper fraction.52% patients presented with main complaint of pain and 32% of patients with dysphagia, after radiotherapy more than 76% got relief from pain and more than 66% patients got relief from dysphagia. Further radiotherapy was given according to the tumor regression status of palliative radiotherapy.

However concurrent chemo radiation can be tried in these patients as a dose escalation after palliative radiotherapy. In this study, after initial palliative radiotherapy with high dose per fractionation, appreciable palliation and partial response was achieved in majority of the patients. Tumor burden and distressing symptoms was minimized some extent after palliative radiotherapy. So, these patients were given chemo radiation for curative intent.

PREVIOUS DOSE ESCALATION STUDIES

Ali My et[44] al conducted a study comprising 30 locally advanced SCCHN patients who were treated initially by palliative radiotherapy 30 Gy in 3 Gy per fractions. Patients achieving >50% symptom relief and partial response at primary and nodal site and in good general condition after one month of palliative radiotherapy were taken up for further radiotherapy with curative intent. Further radiotherapy was given in 2 Gy per fractions upto a total radiobiologically equivalent dose of 66 Gray with same radiation portals that were used in PRT.

Spinal cord shielding was done at 40 Gy. It was calculated by Time-Dose-Fractionation (TDF) method taking into account the dose fraction of palliative radiotherapy with gap correction.

Following studies are supporting the dose escalation of this study.

Table -27PREVIOUS STUDIES

Study name	Radiotherapy dose used	No.of.patients showed partaial response	No.of patients given further radiotherapy
Mohanti et al[39] (n= 505)	20 Gy, 4Gy/#,5#	189(37%)	153(30%)
Ali My et al[44] (n=30)	30Gy,3Gy/#,10#	14 (47%), CR-8(27%)	8 (27%)
Rajan Paliwal et al[42] (n=50)	20 Gy,4Gy/#,5#	46 (92%), CR-4(8%)	Further RT given (number not mentioned)

Mohanti et al [39] conducted a study on 505 patients with stage IV SCCHN. All patients were given 20 Gray of palliative radiotherapy, 4Gray/#, 5 # over one week. 70% percent of cases complained of two or more distressing symptoms at presentation. On assessment at one month after the palliative radiotherapy, 189 patients (37%) attained a partial response and had ambulatory physical state well suited for further radiotherapy with intent. Good symptom relief (50% or more) was seen in 57% for pain, 53% for difficulty in swallowing, 57% for voice change, 47% for ear pain, 76% for dyspnoea and 59% for cough. The main acute toxicity of Palliative radiotherapy was

grade II mucositis and dermatitis. Median overall survival was 200 and 400 days in patients receiving palliative radiotherapy and further radiotherapy respectively.

In the present study complete response rate after chemo radiation was seen in 3 out 30 study patients (10%).

Mohanti et al[39]. alsorecorded the same that around 10 % of the patients were disease free after further radiotherapy.

Toxicity

Previous studies has concluded that due to palliative nature of the treatment, late tissue toxicities were not a significant problem in the patients received short course palliative radiotherapy. Significant chronic xerostomia and other late toxicities of evaluable patients were acceptable and were not dose dependant. So patients received further radiotherapy did not have any worst late toxicity as compared to patients received initial palliative radiotherapy alone.

In the present study, more than 50 % symptom relief was noted in 80% of the patients with pain, 73% of the patients with dysphagia, 70% of the patients with cough, 66% of the patients with otalgia, 75% of the patients with

dyspnoea, 40% of the patients with voice change and 78% of the patients with insomnia. The main acute toxicity of palliative radiotherapy was more or less same to the above mentioned studies. Assessment at 1 month after palliative radiotherapy showed partial response rate of 76.6% (n=23).

In the present study, majority of the cases presented with multiple symptoms and the short course of palliative radiotherapy offered appreciable symptom relief quickly in these patients.

Further chemo radiotherapy was given in 53% (n=16)of the patients. These patients were tolerated further chemo radiotherapy reasonably. None of them developed grade III or more toxicities. No one was died due to treatment toxicity. Among 16 patients who received further chemo radiotherapy, 3 patients showed complete response at 1 month post chemo radiotherapy. Supportive care was given to the remaining patients.

In summary the present study shows that hypofractionated short course palliative radiotherapy is better and effective for unresectable ,advanced and poor PS (Performance Status) patients. This study also helps in finding the patients for further chemo radiotherapy.

Limitations of the study

It is a known fact that even a single day of delay in the radiotherapy schedule is detrimental to the final outcome due to tumor re-population. In this study there was a treatment gap of 1 month between palliative radiotherapy and further chemo radiotherapy with curative intent. Because of that treatment delay and also due to extensive disease burden, majority of the patients left with residual disease after further chemo radiotherapy. Only 10 % of the study patients(n=30) were disease free after further chemo radiotherapy. However, it (tumor repopulation) is not a major issue in a palliative setting.

There was no long term follow up of the patient which would have given the duration of symptom relief and overall survival of the patients.

CONCLUSION

CONCLUSION

In conclusion, head and neck cancers are the major public health problem in a developing country like India. Most of these patients presented with the advanced and unresectable stages. Most of them are not suitable for aggressive multi modality radical chemo radiotherapy or long duration palliative radiotherapy because of poor general condition of the patients and incurable nature of the disease. So short course hypofractionated radiation is effective for palliation to relieve the symptoms quickly with manageable side effects in these advanced and unresectable HNC cases.

As we see in the present study, short course palliative radiotherapy can effectively restrain the growth, relieve symptoms and thereby increases the quality of life of the patients.

This study also helps in selecting the patients for further chemo radiotherapy based on tumor regression and symptom relief after palliative radiotherapy.

Also, this study is trying to strike a balance between economic burden, treatment time and hospital stay and machine load.

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ANNEXURES

ANNEXURE I

HEMATOLOGICAL TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-

ANNEXURE II

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

CTCAE VERSION 4.

GRADE	1	2	3	4	5
NAUSEA	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition.	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated.	-	-

Grade	1	2	3	4	5
vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tubefeeding,TPN or hospitalization indicated	Life-threatening consequences,urgent intervention indicated	death

ANNEXURE III

INFORMATION SHEET

- You have been accepted by the Department of Radiotherapy to enroll into the study "SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER"

- We are conducting a study on head and neck cancers among patients attending Government General Hospital, Chennai.

- The purpose of this study is to find if prior treatment of chemotherapy followed by concurrent chemoradiation will have a better response rates and lower recurrences.

- We are selecting certain cases and if your case is found eligible, we may be performing extra tests and special studies which in any way do not decrease your chance of optimum treatment.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

ANNEXURE IV

INFORMED CONSENT FORM

TITLE OF THE STUDY: "SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER"

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPLE (Co – Investigator) : DR.S.VIJAYAKUMAR

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I,_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "SHORT COURSE PALLIATIVE RADIOTHERAPY IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER"

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have informed the investigator of all the treatments I am taking or have taken in the past_____ months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.*

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer

unusual symptoms. *

8. I have not participated in any research study within the past _____month(s). *

9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *

11. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

12. I understand that my identity will be kept confidential if my data are publicly presented

13. I have had my questions answered to my satisfaction.

14. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the participant

Name _____ Signature_____
Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____
Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

ANNEXURE V

<u>ஆராய்ச்சி தகவல் தாள்:</u>

ஆராய்ச்சியின் பெயர்

தலை மற்றும் கழுத்து பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்த பிறகு நான் குவாரங்கள் கழித்து ,கதிர் வீசின் பலனை ஆராய் நது பலனுக் கேற்ப தேவைப் படின் மீண் டும்ஒரு மாத காலத்திற்கு கதிர்வீச்சு சிகிச்சையுடன் புற் றுநோய் மருந்தும அளித்து புற்றுநோயை குணப்படுத்த முயற்சிப்பது பற் றிய ஆய்வு.

சென்னை இராஜீவ்காந்தி அரசு பொது ம ருத்துவமனைக்கு வரும் புற்று நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சைப் பற்றிய ஆராய்ச்சி.

தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய்க்கு பல வகையான கதிர்வீச்சு சிகிச்சை முறைகள் உ ள்ளன. அவற்றுள் குணப்படுத்த முடியாத மிகவும் முற்றிய புற்றுநோய்க்கு முதலில் ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்த பிறகு நான் குவாரங்கள் கழித்து ,கதிர் வீசசின் பலனை ஆராய்நது பலனுக் கேற்ப தேவைப் படின் மீண் டும்ஒரு மாத காலத்திற்கு கதிர்வீச்சு சிகிச்சையுடன் புற் றுநோய் மருந்துஅளித்து புற்றுநோயை குணப்படுத்த முயற்சிப்பதுஇந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உ ட்படுத்தி அதன் தகவல்களை ஆராய்வோம். இதனால் தங்கள் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு எற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்
தேதி: தேதி:

ANNEXURE VI

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சியாளர் பெயர்: தேதி:

வயது: உள்/புற நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

பங்கேற்பாளர் பெயர்:

தலை மற்றும் கழுத்து பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்த பிறகுநான்குவாரங்கள் கழித்து ,கதிர் வீசின் பலனை ஆராய்ந்து பலனுக் கேற்ப தேவைப் படின மீண் டுமஒரு மாத காலத்திற்கு கதிர்வீச்சு சிகிச்சையுடன் புற் றுநோய மருந்தும அளித்துபுற்றுநோயை குணப்படுத்த முயற்சியது பற்றிய ஆய்வு.

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு விளக்கப்பட்டன.

எனக்கு விளக்கப்பட்ட விவரங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சை செய்து கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் பங்கு பெறுகிறேன்.இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்று நோய் குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை மற்றும்புற்று நோய்மருந்துபெற்றுக் கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும் , சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

நான் என்னுடைய சுயநினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்
தேதி: தேதி:

ANNEXURE VII

ETHICAL COMMITTEE CLEARANCE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. S. Vijaya Kumar,
PG in Radio Therapy,
Department of Radio Therapy,
Madras Medical College, Chennai-3.

Dear Dr. S. Vijaya Kumar,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Short Course Palliative Radiotherapy followed by Chemoradiation with Curative Intent in Advanced and Unresectable Head and Neck Cancer"** No.06032014

The following members of Ethics Committee were present in the meeting held on 11.03.2014 conducted at Madras Medical College, Chennai-3.

1. Dr. C. Rajendran, M.D.	-- Chairperson
2. Dr. R. Vimala, M.D. Dean, MMC, Ch-3.	-- Deputy Chairperson
3. Prof. Kalaiselvi, MD Vice-Principal, MMC, Ch-3	-- Member Secretary
4. Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5. Prof. Bhavani Shankar, M.S. Prof & HOD of General Surgery, MMC, Ch-3.	-- Member
6. Prof. V. Padmavathi, M.D. I/c Director of Pathology, MMC, Ch-3.	-- Member
7. Thiru. S. Govindasamy, BABL	-- Lawyer
8. Tmt. Arnold Saulina, MA MSW	-- Social Scientist
9. Thiru. S. Ramesh Kumar, Administrative Officer, MMC, Ch-3.	-- Layperson

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

13/3/14

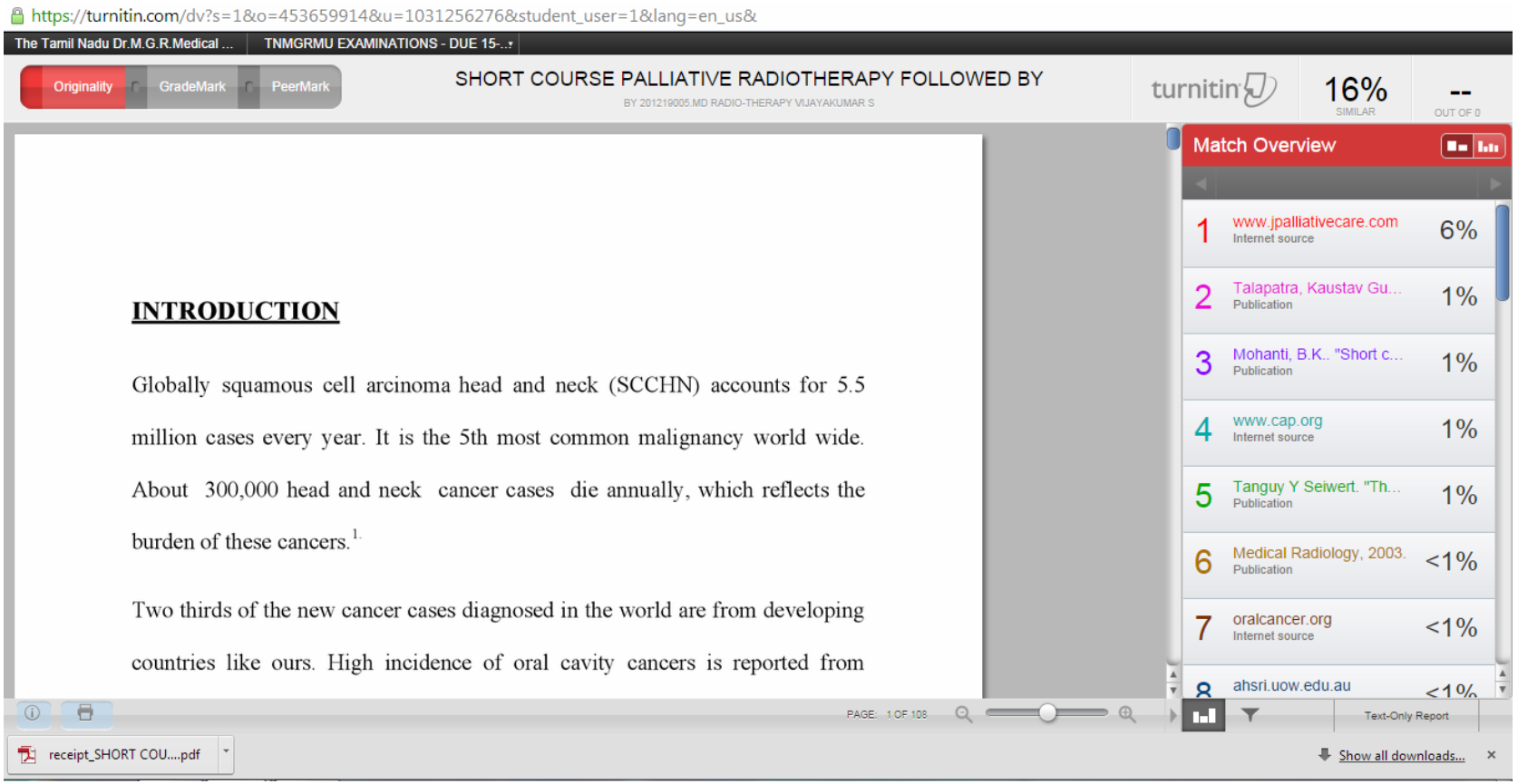
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

13/3/14

ANNEXURE VIII

ORIGINALITY CERTIFICATE



ANNEXURE IX

SHORT COURSE PALLIATIVE RADIOTHERAPY FOLLOWED BY CHEMORADIATION WITH CURATIVE INTENT IN ADVANCED AND UNRESECTABLE HEAD AND NECK CANCER

ORIGINALITY REPORT

16%	10%	15%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.jpalliativecare.com Internet Source	6%
2	Talapatra, Kaustav Gupta, Tejpal Agarwal. "Palliative radiotherapy in head and neck cancers: Evidence based review.(Review Article)", Indian Journal of Palliative Care, July-Dec 2006 Issue Publication	1%
3	Mohanti, B.K.. "Short course palliative radiotherapy of 20Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study", Radiotherapy and Oncology, 200406 Publication	1%
4	www.cap.org Internet Source	1%
5	Tanguy Y Seiwert. "The chemoradiation paradigm in head and neck cancer", Nature Clinical Practice Oncology, 03/2007 Publication	1%